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(74) Agents: STEFFEY, Charles, E. et al.; Schwegman, Lundberg, Woessner &amp; Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).

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(71) Applicant (*for all designated States except US*): CELL-TECH R & D, INC. [US/US]; 1631 220th Street S.E., Bothell, WA 98021 (US).

(71) Applicants and

(72) Inventors: RAMSDELL, Fred [US/US]; 9891 NE Day Road, Bainbridge Island, WA 98110 (US). PROLL, Sean, C. [US/US]; 8211 22nd Avenue N.E., Seattle, WA 98115 (US). STAELING-HAMPTON, Karen [US/US]; 2521 181st Place S.E., Bothell, WA 98019 (US). APPELBY, Mark, W. [GB/US]; 16211 15th Avenue N.E., Shoreline, WA 98155 (US). MARTINEZ, Leon, Fernando, Garcia [MX/US]; 4926 214th S.E., Woodinville, WA 98072 (US).

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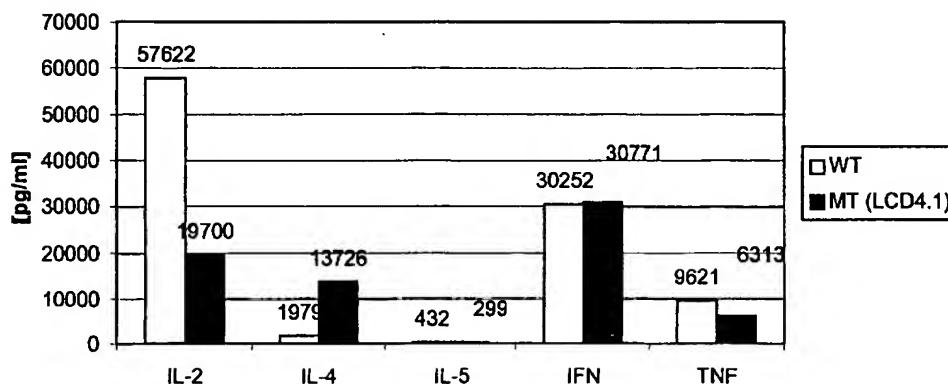
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(54) Title: MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS



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(57) Abstract: The invention provides methods for modulating cytokine levels, GM-CSF levels and the immune system using CD83 nucleic acids, CD83 polypeptides, anti-CD83 antibodies and factors that influence CD83 activity or expression. The invention also provides mice having a mutant CD83 gene and mice having a transgenic CD83 gene, which are useful for defining the role of CD83 in the immune system and for identifying compounds that can modulate CD83 and the immune system.

**MANIPULATION OF CYTOKINE LEVELS**  
**USING CD83 GENE PRODUCTS**

5        This application is related to U.S. Application Ser. No. 60/331,958 filed  
November 21, 2001.

**FIELD OF THE INVENTION**

The invention relates to an altered CD83 gene product, and methods of  
10 modulating cytokine levels by modulating the expression of mutant and wild  
type CD83 gene products produced in a mammal. The invention also relates to  
the regulation of T cell and dendritic cell activity and conditions and treatments  
related thereto.

15        **BACKGROUND OF THE INVENTION**

CD83 is a 45 kilodalton glycoprotein that is predominantly expressed on  
the surface of dendritic cells and other cells of the immune system. Structural  
analysis of the predicted amino acid sequence of CD83 indicates that it is a  
member of the immunoglobulin superfamily. See, Zhou et al., J. Immunol.  
20 149:735 (1992)). U.S. Patent 5,316,920 and WO 95/29236 disclose further  
information about CD83. While such information suggests that CD83 plays a  
role in the immune system, that role is undefined, and the interrelationship of  
CD83 with cellular factors remains unclear.

Moreover, treatment of many diseases could benefit from more effective  
25 methods for increasing or decreasing the immune response. Hence, further  
information about how to modulate the immune system by using factors such as  
CD83 are needed.

**SUMMARY OF THE INVENTION**

30        The invention provides a method of modulating cytokine levels by  
modulating the activity or expression of the CD83 gene products. According to  
the invention, cytokine levels can be modulated in a mammal or in mammalian

cells that are involved in the immune response, for example, antigen presenting cells or T cells.

The invention therefore provides a method of modulating cytokine production in a mammal or in an immune cell by modulating the activity or expression of a CD83 polypeptide. According to the invention, the production of a cytokine such as interleukin-2, interleukin-4, or interleukin-10 can be modulated by modulating the activity or expression of a CD83 polypeptide. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating granulocyte macrophage colony stimulating factor production in a mammal or in an immune cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating tumor necrosis factor production in a mammal or in a mammalian cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the mammalian cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention further provides a method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For

example, the antibody can be administered to the mammal or the human peripheral blood mononuclear cell can be contacted with the antibody.

The invention also provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein activated CD4<sup>+</sup> T-cells produce lower levels of interleukin-4 when the T-cells are contacted with the antibody. The invention further provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein CD4<sup>+</sup> T-cells proliferation is decreased when the T-cells are contacted with the antibody. Such an antibody can have an amino acid sequence that includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64. Nucleic acids encoding such an antibody can have, for example, a sequence that includes SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63 or SEQID NO:65.

The invention also provides a method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID

NO:62 or SEQ ID NO:64. The activity of a CD83 gene product can be decreased in a mammal or in a cell that is involved in an immune response, for example, a T cell.

The invention further provides a method for decreasing the translation of  
5 a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

In another embodiment, the invention provides a method for decreasing the translation of a CD83 gene product in a mammal, comprising administering  
10 to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention further provides a method for decreasing proliferation of CD4+ T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product  
15 comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34,  
20 SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ  
25 ID NO:64.

The invention also provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have  
30 a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID

NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ 5 ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising 10 SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments the interleukin-2 levels are decreased and the interleukin-4 levels are increased to treat an autoimmune disease. In other embodiments, the interleukin-2 levels are decreased and the interleukin-4 levels are increased to stimulate production of Th2-associated cytokines in transplant recipients, for 15 example, to prolong survival of transplanted tissues.

The invention also provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID 20 NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, 25 SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for increasing interleukin-10 30 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments, the interleukin-

10 levels are increased to treat neoplastic disease. In other embodiments, the interleukin-10 levels are increased to treat a tumor.

The invention also provides a method for increasing interleukin-2 levels in a mammal comprising administering to the mammal a functional CD83 5 polypeptide that comprises SEQ ID NO:9.

The invention further provides a method for increasing interleukin-2 levels in a mammal comprising: (a) transforming a T cell from the mammal with a nucleic acid encoding a functional CD83 polypeptide operably linked to a promoter functional in a mammalian cell, to generate a transformed T cell; (b) 10 administering the transformed T cell to the mammal to provide increased levels of interleukin-2. In some embodiments, the CD83 polypeptide has a sequence that comprises SEQ ID NO:9 or the nucleic acid has a sequence that comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. Such methods for increasing interleukin-2 levels can be used to treat an allergy or an infectious 15 disease.

The invention also provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

20 Such an antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, 25 SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

30 The invention further provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic

acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention also provides a method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide. In another embodiment, the invention provides a method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide. The CD83 polypeptide employed can, for example, have a sequence comprising SEQ ID NO:9.

Mammals and birds may be treated by the methods and compositions described and claimed herein. Such mammals and birds include humans, dogs, cats, and livestock, for example, horses, cattle, sheep, goats, chickens, turkeys and the like.

The invention further provides a mutant mouse that can serve as an animal model of diminished T cell activation or altered cytokine levels. The mutant mouse has an altered CD83 gene that produces a larger gene product, having SEQ ID NO:4 or containing SEQ ID NO:8. Also provided are methods of using the mutant mouse model to study the effects of cytokines on the immune system, inflammation, the function and regulation of CD83, T cell and dendritic cell activity, the immune response and conditions and treatments related thereto. Hence, the invention further provides a mutant mouse whose somatic and germ cells comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of the mutant CD83 gene reduces CD4+T cell activation. The mutant CD83 gene can, for example, comprise SEQ ID NO:3.

The invention further provides a method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mouse having a mutant or wild type transgenic CD83 gene and observing whether CD4+ T cell activation is decreased or increased. The somatic and/or germ cells of the mutant mouse can comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. Alternatively, the somatic and/or germ cells of the mouse can contain a wild type CD83 gene, for example, SEQ ID NO:1 or SEQ ID NO:9.

The invention also provides a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. The invention further provides a mutant CD83 gene comprising nucleotide sequence SEQ ID NO:3.

## 5 DESCRIPTION OF THE FIGURES

Figure 1 provides flow cytometry data for G3 animals. As shown, reduced numbers of CD4+ T cells are seen in two animals from Pedigree 9, mouse 9.4.1 and mouse 9.4.9. All other animals analyzed on that day exhibit normal numbers of CD4+ T cells.

10 Figure 2 provides a graph of flow cytometry data for G3 animals. Each diamond symbol represents an individual animal. As shown, multiple animals from the N2 generation exhibit a reduced percentage of CD4+ T cells.

Figure 3 provides the nucleotide sequence of wild type mouse CD83 (SEQ ID NO:1). The ATG start codon and the TGA stop codon are underlined.

15 Figure 4A-B provides the nucleotide sequence of the mutant CD83 gene (SEQ ID NO:3) of the invention derived from the mutant LCD4.1 animal. The ATG start codon, the mutation and the TGA stop codon are underlined.

20 Figure 5 provides the amino acid sequence for wild type (top, SEQ ID NO:2) and mutant (bottom, SEQ ID NO:4) CD83 coding regions. The additional C-terminal sequences arising because of the CD83 mutation are underlined.

Figure 6A illustrates that dendritic cells from wild type (♦, WT DC) and mutant (■, mutant DC) mice are capable of the allogeneic activation of CD4+ T cells. CD4+ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

25 Figure 6B illustrates that CD4+ T cells from mutant mice (■, mutant CD4) fail to respond to allogeneic stimulation with BALBc dendritic cells, although wild type animals (♦, WT CD4+) respond normally. CD4+ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

30 Figure 7 provides a bar graph illustrating IL-2, IL-4, IL-5, TNF $\alpha$ , and IFN $\gamma$  production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 1  $\mu$ g/ml of anti-CD3 antibodies

and 0.2  $\mu$ g/ml of anti-CD28 antibodies for 72 hours. As illustrated, IL-2 levels are lower, and IL-4 levels are higher in the CD83 mutant T cells.

Figure 8 provides a bar graph illustrating IL-10 production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 0.1  $\mu$ g/ml of anti-CD28 antibodies and 1 to 10  $\mu$ g/ml of anti-CD3 antibodies for 72 hours. As illustrated, IL-10 levels are higher in the CD83 mutant T cells.

Figure 9 provides a bar graph illustrating GM-CSF production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, GM-CSF production is higher in the CD83 mutant cells than in wild type cells.

Figure 10A provides a bar graph illustrating IL-4 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-4 mRNA levels are higher in the CD83 mutant cells.

Figure 10B provides a bar graph illustrating IL-10 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-10 mRNA levels are higher in the CD83 mutant cells.

Figure 11 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit IL-4 production in anti-CD3 and anti-CD28 antibody stimulated T cells. The amount of IL-4 produced by T cells in pg/ml is plotted versus the concentration of different anti-CD83 antibody preparations, including the 20B08 (♦) anti-CD83 preparation, the 20D04 (■) anti-CD83 preparation, the 14C12 (▲) anti-CD83 preparation and the 11G05 (X) anti-CD83 antibody preparation.

Figure 12 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpm's, which was used as an indicator of the amount of T cell proliferation, versus the concentration of the different anti-CD83 antibody preparations, including the 20D04 (♦) anti-CD83 preparation, the 11G05 (■) anti-CD83 antibody preparation, the 14C12 (▲) anti-CD83 preparation and the 6G05 anti-CD83 preparation (X).

Figure 13 provides a graph illustrating that transgenic mice that over-express wild type CD83 have increased T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpm's, which was used as an indicator of the amount of T cell proliferation, versus the concentration of OVA peptide.

5    The transgenic mice utilized had a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide that can activate T-cells. When mixed with either transgenic or wild type dendritic cells in the presence of OVA peptide, transgenic CD4+ T cells had increased T-cell proliferation. However, transgenic dendritic cells could not substantially increase wild type CD4+ T cell proliferation.

10   Transgenic CD83 CD4+ T cells mixed with wild type dendritic cells (♦); transgenic CD83 CD4+ T cells mixed with transgenic dendritic cells (■); wild type CD4+ T cells mixed with transgenic dendritic cells (▲); and wild type CD4+ T cells mixed with wild type dendritic cells (X).

15   Figure 14 provides a schematic diagram of the structural elements included in the mouse CD83 protein used for generating antibodies.

Figure 15 provides a graph of ELISA data illustrating the titer obtained for different isolates of polyclonal anti-CD83 anti-sera. The first (♦), second (■) and third (▲) isolates had similar titers, though the titer of the second isolate (■) was somewhat higher.

20   Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein (♦). Pre-immune serum (■) had little effect on the proliferation of human PBMCs.

25   Figure 17A provides a sequence alignment of anti-CD83 heavy chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:52), 6G05H (SEQ ID NO:53), 20D04H (SEQ ID NO:54), 11G05 (SEQ ID NO:66) and 14C12 (SEQ ID NO:67) are provided. The CDR regions are highlighted in bold.

30   Figure 17B provides a sequence alignment of anti-CD83 light chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:55), 6G05H (SEQ ID NO:56), 20D04H (SEQ ID NO:57), 11G05 (SEQ ID NO:68) and 14C12 (SEQ ID NO:69) are provided. The CDR regions are highlighted in bold.

**DETAILED DESCRIPTION OF THE INVENTION**

The invention provides methods for modulating the immune system by using CD83 proteins, CD83 nucleic acids and factors that modulate CD83 activity or expression.

According to the invention, loss or reduction of CD83 activity *in vivo* results in altered cytokine levels, for example, lower interleukin-2 levels, increased interleukin-4 levels, increased GM-CSF levels and increased interleukin-10 levels. Loss or reduction of CD83 activity *in vivo* can also result in decreased numbers of T cells.

Moreover, the invention also relates to increased CD83 activity *in vivo* that can result in altered cytokine levels, for example, higher interleukin-2 levels, decreased interleukin-4 levels, decreased GM-CSF levels and decreased interleukin-10 levels. Increased CD83 expression or activity *in vitro* and *in vivo* can also result in increased activation and increased numbers of T cells.

The effects of CD83 on the immune system, on GM-CSF and on cytokine levels were analyzed by using mutant and transgenic mice. The mutant mouse has an altered CD83 gene that expresses altered (defective) CD83 gene product. The transgenic mouse overexpresses CD83 gene products. Accordingly, the invention provides mammals such as mice that have a mutant or wild type CD83 gene. These mice are useful for identifying the role that CD83 plays in the immune response. These mutant and transgenic animals are useful for identifying factors for manipulating cytokine levels and T cell activation by testing whether those factors and compositions can modulate, inhibit or replace the activity of CD83 *in vivo*.

**CD83**

CD83 is a lymphocyte and dendritic cell activation antigen that is expressed by activated lymphocytes and dendritic cells. CD83 is also a single-chain cell-surface glycoprotein with a molecular weight of about 45,000 that is believed to be a member of the Ig superfamily. The structure predicted from the CD83 amino acid sequence indicates that CD83 is a membrane glycoprotein with a single extracellular Ig-like domain, a transmembrane domain and cytoplasmic

domain of approximately forty amino acids. The mature CD83 protein has about 186 amino acids and is composed of a single extracellular V type immunoglobulin (Ig)-like domain, a transmembrane domain and a thirty nine amino acid cytoplasmic domain. Northern blot analysis has revealed that CD83 5 is translated from three mRNA transcripts of about 1.7, 2.0 and 2.5 kb that are expressed by lymphoblastoid cell lines. It is likely that CD83 undergoes extensive post-translational processing because CD83 is expressed as a single chain molecule, but the determined molecular weight is twice the predicted size of the core protein. *See* U.S. Patent 5,766,570.

10 An example of a human CD83 gene product that can be used in the invention is provided below (SEQ ID NO:9):

```
1 MSRGLQLLLL SCAYSLAPAT PEVKVACSED VDL PCTAPWD  
41 PQVPYTVSWV KLLEGGEERM ETPQEDHLRG QHYHQKGQNG  
81 SFDAPNERPY SLKIRNTTSC NSGTYRCTLQ DPDGQRNLSG  
15 121 KVILRVTGCP AQRKEETFKK YRAEIVLLLA LVIFYLTLII  
161 FTCKFARLQS IFPDFSKAGM ERAFLPVTSP NKHLGLVTPH  
201 KTELV
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Such a CD83 gene product can be encoded by a number of different nucleic 20 acids. One example of a human CD83 nucleic acid is provided below (SEQ ID NO:10).

```
1 CCTGGCGCAG CCGCAGCAGC GACGCGAGCG AACTCGGCCG  
41 GGCCCGGGCG CGCGGGGGCG GGACCGCGAC GCGGCGAGGG  
81 CGGCGGGTGA GCCGGGGCG GGGACGGGG CGGGACGGGG  
25 121 GCGAAGGGGG CGGGGACGGG GGCGCCCGCC GGCTAACGG  
161 GATTAGGAGG GCGCGCCACC CGCTTCCGCT GCCCGCCGGG  
201 GAATCCCCG GGTGGCGCCC AGGGAAGTTC CCGAACGGGC  
241 GGGCATAAAAA GGGCAGCCGC GCCGGCGCCC CACAGCTCTG  
281 CAGCTCGTGG CAGCGGCGCA GCGCTCCAGC CATGTCGCGC  
30 321 GGCTCCAGC TTCTGCTCCT GAGCTGCGCC TACAGCCTGG  
361 CTCCCGCGAC GCCGGAGGTG AAGGTGGCTT GCTCCGAAGA  
401 TGTGGACTTG CCCTGCACCG CCCCCCTGGGA TCCGCAGGTT  
441 CCCTACACGG TCTCCTGGGT CAAGTTATTG GAGGGTGGTG  
481 AAGAGAGGAT GGAGACACCC CAGGAAGACC ACCTCAGGGG  
35 521 ACAGCACTAT CATCAGAAGG GGCAAAATGG TTCTTCGAC
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561 GCCCCCAATG AAAGGCCCTA TTCCCTGAAG ATCCGAAACA  
601 CTACCAGCTG CAACTCGGGG ACATACAGGT GCACTCTGCA  
641 GGACCCGGAT GGGCAGAGAA ACCTAAGTGG CAAGGTGATC  
681 TTGAGAGTGA CAGGATGCC TGACACAGCGT AAAGAAGAGA  
5 721 CTTTTAAGAA ATACAGAGCG GAGATTGTCC TGCTGCTGGC  
761 TCTGGTTATT TTCTACTTAA CACTCATCAT TTTCACTTGT  
801 AAGTTGCAC GGCTACAGAG TATCTTCCA GATTTTTCTA  
841 AAGCTGGCAT GGAACGAGCT TTTCTCCCAG TTACCTCCCC  
881 AAATAAGCAT TTAGGGCTAG TGACTCCTCA CAAGACAGAA  
10 921 CTGGTATGAG CAGGATTCT GCAGGTTCTT CTTCCTGAAG  
961 CTGAGGCTCA GGGGTGTGCC TGTCTGTTAC ACTGGAGGAG  
1001 AGAAGAATGA GCCTACGCTG AAGATGGCAT CCTGTGAAGT  
1041 CCTTCACCTC ACTGAAAACA TCTGGAAGGG GATCCCACCC  
1081 CATTTCTGT GGGCAGGCCT CGAAAACCAT CACATGACCA  
15 1121 CATAGCATGA GGCCACTGCT GCTTCTCCAT GGCCACCTTT  
1161 TCAGCGATGT ATGCAGCTAT CTGGTCAACC TCCTGGACAT  
1201 TTTTCAGTC ATATAAAAGC TATGGTGAGA TGCAGCTGGA  
1241 AAAGGGCTT GGGAAATATG AATGCCCCA GCTGGCCCGT  
1281 GACAGACTCC TGAGGGACAGC TGTCCCTTC TGCATCTTGG  
20 1321 GGACATCTCT TTGAATTTTC TGTGTTTGC TGTACCAAGCC  
1361 CAGATGTTTT ACGTCTGGGA GAAATTGACA GATCAAGCTG  
1401 TGAGACAGTG GGAAATATTT AGCAAATAAT TTCCTGGTGT  
1441 GAAGGTCCTG CTATTACTAA GGAGTAATCT GTGTACAAAG  
1481 AAATAACAAG TCGATGAACT ATTCCCCAGC AGGGTCTTTT  
25 1521 CATCTGGAA AGACATCCAT AAAGAAGCAA TAAAGAAGAG  
1561 TGCCACATTT ATTTTATAT CTATATGTAC TTGTCAAAGA  
1601 AGGTTGTGT TTTCTGCTT TTGAAATCTG TATCTGTAGT  
1641 GAGATAGCAT TGTGAACCTGA CAGGCAGCCT GGACATAGAG  
1681 AGGGAGAAGA AGTCAGAGAG GGTGACAAGA TAGAGAGCTA  
30 1721 TTTAATGGCC GGCTGGAAAT GCTGGGCTGA CGGTGCAGTC  
1761 TGGGTGCTCG CCCACTTGTC CCACTATCTG GGTGCATGAT  
1801 CTTGAGCAAG TTCCCTCTGG TGTCTGCTTT CTCCATTGTA  
1841 AACCAACAAG CTGTTGCATG GGCTAATGAA GATCATATAC  
1881 GTGAAAATTA TTTGAAAACA TATAAAGCAC TATACAGATT  
35 1921 CGAAACTCCA TTGAGTCATT ATCCTTGCTA TGATGATGGT  
1961 GTTTTGGGGA TGAGAGGGTG CTATCCATT CTCATGTTT

2001 CCATTGTTG AAACAAAGAA GGTTACCAAG AAGCCTTCC  
 2041 TGTAGCCTTC TGTAGGAATT CTTTGCGGA AGTGAGGAAG  
 2081 CCAGGTCCAC GGTCTGTTCT TGAAGCAGTA GCCTAACACA  
 2121 CTCCAAGATA TGGACACACCG GGAGCCGCTG GCAGAAGGGA  
 5 2161 CTTCACGAAG TGGTGCATGG ATGTTTAGC CATTGTTGGC  
 2201 TTTCCCTTAT CAAACTTGGG CCCTTCCCTT CTTGGTTTCC  
 2241 AAAGGCATTT ATTGCTGAGT TATATGTTCA CTGTCCCCCT  
 2281 AATATTAGGG AGTAAAACGG ATACCAAAGTT GATTTAGTGT  
 2321 TTTTACCTCT GTCTTGGCTT TCATGTTATT AAACGTATGC  
 10 2361 ATGTGAAGAA GGGTGTTTT CTGTTTATA TTCAACTCAT  
 2401 AAGACTTTGG GATAGGAAAA ATGAGTAATG GTTACTAGGC  
 2441 TTAATACCTG GGTGATTACA TAATCTGTAC AACGAACCCC  
 2481 CATGATGTAA GTTTACCTAT GTAACAAACC TGCACTTATA  
 2521 CCCATGAAC TAAAATGAAA GTTAAAAATA AAAAACATAT  
 15 2561 ACAAATAAAA AAAA

A sequence of a wild type mouse CD83 gene that can be used in the invention is provided herein as SEQ ID NO:1. SEQ ID NO:1 is provided below with the ATG start codon and the TGA stop codon identified by underlining.

20  
 1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTT  
 41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC  
 81 GGGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC  
 121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG  
 25 161 TCCTGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG  
 201 AGCTCCCGA GAGCAAGCAA AACAGCTCCT TCGAGGCC  
 241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AACACACTACC  
 281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC  
 321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA  
 30 361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC  
 401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG  
 441 TTGTTTCTA CCTGACACTC ATCATTTCCTA CCTGCAAATT  
 481 TGCACGACTA CAAAGCATT TCCCAGATAT TTCTAAACCT  
 521 GGTACGGAAC AAGCTTTCT TCCAGTCACC TCCCCAAGCA  
 35 561 AACATTGGG GCCAGTGACC CTTCCCTAAGA CAGAAACGGT  
 601 ATGAGTAGGA TCTCCACTGG TTTTTACAAA GCCAAGGGCA

641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA  
681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT  
721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA  
761 GGGTCTTGAG CACCACATA TGATCACGAA GCATGGAGTA  
5 801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG  
841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC  
881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA  
921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG  
961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTGAA  
10 1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC  
1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA  
1081 TATTTAGCAA ATAATTCCC AGTGCAGG TCCTGCTATT  
1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT  
1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA  
15 1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT  
1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG  
1281 TTTTTCAAA GAAGTGTGTT TCTTTCTTT TTTAAAATAT  
1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC  
1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA  
20 1401 AGCTAGAACG ACTGTACAGT GCCCTGCTGG GAAGGGCAGA  
1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC  
1481 TGTATGATTG TGGACGAGTC ACTTGTGGTT TTCACTCTCT  
1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT  
1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA  
25 1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT  
1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT  
1681 TGCCCACCAA TCCAAACACA GGAGGCTACA AAAAGGACAT  
1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG  
1761 AGACTGGCTC AGCGCTTGC GCTTGAAGGA CTAATCACAA  
30 1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG  
1841 ACAGGAGGAA GTTCTCAGAT GTTGCATTGA TGTAACATTG  
1881 TTGCATTCT TTAATGAGCT GGGCTCCTTC CTCATTGCT  
1921 TCCCCAAAGAG ATTTGTCCC ACTAATGGTG TGCCCAC  
1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC  
35 2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA  
2041 ATGCATGTGA A

Nucleic acids having SEQ ID NO:1 encode a mouse polypeptide having SEQ ID NO:2, provided below.

5       1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP  
41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA  
81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTGC  
121 PKEATESTF R KYRAEAVLLF SLVVFYLTLL IIFTCKFARLQ  
161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV

10

According to the invention, loss or reduction of CD83 activity *in vivo* results in altered cytokine levels, for example, lower interleukin-2 levels, increased interleukin-4 levels, increased GM-CSF levels and increased interleukin-10 levels. Loss or reduction of CD83 activity *in vivo* can also result in decreased numbers of T cells.

Moreover, increased CD83 activity *in vivo* can also result in altered cytokine levels, for example, higher interleukin-2 levels, decreased interleukin-4 levels, decreased GM-CSF levels and decreased interleukin-10 levels. Increased CD83 expression or activity *in vivo* can also result in increased activation or increased numbers of T cells.

The effect of CD83 on cytokine levels was ascertained through use of a mutant mouse that encodes a mutant CD83. Such a mutant mouse has a CD83 gene encoding SEQ ID NO:4, with added C-terminal sequences provided by SEQ ID NO:8. In contrast to these wild type CD83 nucleic acids and polypeptides, the mutant CD83 gene of the invention has SEQ ID NO:3. SEQ ID NO:3 is provided below with the ATG start codon, the mutation, and the TGA stop codon are identified by underlining.

1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT  
41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC  
30 81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC  
121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG  
161 TCCTGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG  
201 AGCTCCCGA GAGCAAGCAA AACAGCTCCT TCGAGGCC  
241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC

281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC  
321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA  
361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC  
401 AGGAAGTACA GGGCAGAACGC TGTGTTGCTC TTCTCTCTGG  
5 441 TTGTTTCTA CCTGACACTC ATCATTTCATA CCTGCAAATT  
481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT  
521 GGTACCGGAAC AAGCTTTCT TCCAGTCACC TCCCCAAGCA  
561 AACATTGGG GCCAGTGACC CTTCTAAGA CAGAAACGGT  
601 AAGAGTAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA  
10 641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA  
681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT  
721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA  
761 GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA  
801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG  
15 841 GCTATCTGGT CAACCTCGTG AGTGTTTTC AGTCATCTAC  
881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGAAA  
921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG  
961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTGAA  
1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC  
20 1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGAAA  
1081 TATTTAGCAA ATAATTCCTT AGTGCAGGG TCCTGCTATT  
1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT  
1161 GAACTATTCC CCAGCAGGGC CTTTCATCT GGAAAAGACA  
1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT  
25 1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTCATG  
1281 TTTTTCTAAA GAAGTGTGTT TCTTCTTT TTTAAAATAT  
1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC  
1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA  
1401 AGCTAGAACG ACTGTACAGT GCCCTGCTGG GAAGGGCAGA  
30 1441 CAATGGACTG AGAAACCAGA AGTCTGCCA CAAGATTGTC  
1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TTCACTCTCT  
1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT  
1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA  
1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT  
35 1641 AGAGTTCTGG AGCTGAGCGA ATGCCCTGTCA TATCTCAGCT  
1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT

1721 GAGCATGGTC TTCTGTGTA ACTCCTCCTG AGAAACGTGG  
 1761 AGACTGGCTC AGCGCTTGC GCTTGAAGGA CTAATCACAA  
 1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG  
 1841 ACAGGAGGAA GTTCTCAGAT GTTGATTGA TGTAACATTG  
 5 1881 TTGCATTCT TTAATGAGCT GGGCTCCTTC CTCATTGCT  
 1921 TCCCAGAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC  
 1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC  
 2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA  
 2041 ATGCATGTGA A

10

The change from a thymidine in SEQ ID NO:1 to an adenine in SEQ ID NO:3 at the indicated position (602) leads to read-through translation because the stop codon at positions 602-604 in SEQ ID NO:1 is changed to a codon that encodes an arginine. Accordingly, mutant CD83 nucleic acids having SEQ ID NO:3 encode an elongated polypeptide having SEQ ID NO:4, provided below, where the extra amino acids are underlined.

1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP  
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA  
 20 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTC  
 121 PKEATESTFR KYRAEAVLLF SLVVFYLTG IFTCKFARLQ  
 161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETVRVGS  
 201 PLVFTKPRAH QISVPECHPD KRRMSSILRW QPFPEVLHLT  
 241 VGSTLLPDTG S

25

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:5.

1 ATGTCGCAAG GCCTCCAGCT CCTGTTCTA GGCTGCGCCT  
 30 41 GCAGCCTGGC ACCCGCGATG GCGATGCGGG AGGTGACGGT  
 81 GGCTTGCTCC GAGACCGCCG ACTTGCCCTG CACAGCGCCC  
 121 TGGGACCCGC AGCTCTCTA TGCAGTGTCC TGGGCCAAGG  
 161 TCTCCGAGAG TGGCACTGAG AGTGTGGAGC TCCCGGAGAG  
 201 CAAGCAAAAC AGCTCCTTCG AGGCCCCAG GAGAAGGGCC  
 35 241 TATTCCCTGA CGATCCAAAA CACTACCATC TGCAGCTCGG

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281  GCACCTACAG GTGTGCCCTG CAGGAGCTCG GAGGGCAGCG
321  CAACTTGAGC GGCACCGTGG TTCTGAAGGT GACAGGATGC
361  CCCAAGGAAG CTACAGAGTC AACTTCAGG AAGTACAGGG
401  CAGAAGCTGT GTTGCTCTTC TCTCTGGTTG TTTTCTACCT
5   441  GACACTCATC ATTTTCACCT GCAAATTTGC ACGACTACAA
481  AGCATTTC CAGATATTTC TAAACCTGGT ACGGAACAAG
521  CTTTCTTCC AGTCACCTCC CCAAGCAAAC ATTTGGGCC
561  AGTGACCCTT CCTAAGACAG AAACGGTAAG AGTAGGATCT
601  CCACTGGTTT TTACAAAGCC AAGGGCACAT CAGATCAGTG
10  641  TGCCTGAATG CCACCCGGAC AAGAGAAGAA TGAGCTCCAT
681  CCTCAGATGG CAACCTTC TTGAAGTCCT TCACCTGACA
721  GTGGGCTCCA CACTACTCCC TGACACAGGG TCTTGA

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Nucleic acids having SEQ ID NO:5 also encode a polypeptide having SEQ ID  
15 NO:4.

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:7.

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1   AGAGTAGGAT CTCCACTGGT TTTTACAAAG CCAAGGGCAC
20  41  ATCAGATCAG TGTGCCTGAA TGCCACCCGG ACAAGAGAAG
81   AATGAGCTCC ATCCTCAGAT GGCAACCTTT CTTTGAAGTC
121  CTTCACCTGA CAGTGGGCTC CACACTACTC CCTGACACAG
161  GGTCTTGA

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25 The invention also provides a mutant CD83 containing SEQ ID NO:8, provided below.

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1   RVGSPLVFTK PRAHQISVPE CHPDKRRMSS ILRWQPFFEV
41  LHLTVGSTLL PDTGS

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30 SEQ ID NO:8 contains read through sequences that are not present in the wild type CD83 polypeptide but are present in the mutant CD83 gene product provided by the invention.

#### CD83 Modulation of Cytokine Levels

The invention also provides compositions and methods for increasing interleukin-4 levels, increasing GM-CSF levels, increasing interleukin-10 levels and decreasing interleukin-2 levels in a mammal. Such compositions and methods generally operate by decreasing the expression or function of CD83 gene products in the mammal. Interleukin-4 promotes the differentiation of Th2 cells while decreasing the differentiation of precursor cells into Th1 cells. Th2 cells are involved in helping B lymphocytes and in stimulating production of IgG1 and IgE antibodies. Enhancement of Th2 formation may be useful, for example, in autoimmune diseases and in organ transplantation.

Alternatively, the invention provides compositions and methods for decreasing interleukin-4 levels, decreasing interleukin-10 levels and increasing interleukin-2 levels in a mammal. Such compositions and methods generally increase the expression or function of CD83 gene products in the mammal. Interleukin-2 promotes the differentiation of Th1 cells and decreases the differentiation of Th-2 cells. Th1 cells are, for example, involved in inducing autoimmune and delayed type hypersensitivity responses. Inhibition of Th2 formation may be useful in treating allergic diseases, malignancies and infectious diseases.

CD4+T helper cells are not a homogeneous population but can be divided on the basis of cytokine secretion into at least two subsets termed T helper type 1 (Th1) and T helper type 2 (Th2) (see e.g., Mosmann, T. R. et al. (1986) J. Immunol. 136:2348-2357; Paul, W. E. and Seder, R. A. (1994) Cell 76:241-251; Seder, R. A. and Paul, W. E. (1994) Ann. Rev. Immunol. 12:635-673). Th1 cells secrete interleukin-2 (IL-2) and interferon- $\gamma$  (IFN- $\gamma$ ) while Th2 cells produce interleukin-4 (IL4), interleukin-5 (IL-5), interleukin-10 (IL-10) and interleukin-13 (IL-13). Both subsets produce cytokines such as tumor necrosis factor (TNF) and granulocyte/macrophage-colony stimulating factor (GM-CSF).

In addition to their different pattern of cytokine expression, Th1 and Th2 cells are thought to have differing functional activities. For example, Th1 cells are involved in inducing delayed type hypersensitivity responses, whereas Th2 cells are involved in providing efficient "help" to B lymphocytes and stimulating production of IgG1 and IgE antibodies.

The ratio of Th1 to Th2 cells is highly relevant to the outcome of a wide array of immunologically-mediated clinical diseases including autoimmune, allergic and infectious diseases. For example, in experimental leishmania infections in mice, animals that are resistant to infection mount predominantly a 5 Th1 response, whereas animals that are susceptible to progressive infection mount predominantly a Th2 response (Heinzel, F. P., et al. (1989) *J. Exp. Med.* 169:59-72; Locksley, R. M. and Scott, P. (1992) *Immunoparasitology Today* 1:A58-A6.1). In murine schistosomiasis, a Th1 to Th2 switch is observed coincident with the release of eggs into the tissues by female parasites and is 10 associated with a worsening of the disease condition (Pearce, E. J., et al. (1991) *J. Exp. Med.* 173:159-166; Grzych, J-M.,et al. (1991) *J. Immunol* 141:1322-1327; Kullberg, M. C., et al. (1992) *J. Immunol.* 148:3264-3270).

Many human diseases, including chronic infections (such as with human immunodeficiency virus (HIV) and tuberculosis) and certain metastatic 15 carcinomas, also are characterized by a Th1 to Th2 switch (see e.g., Shearer, G. M. and Clerici, M. (1992) *Prog. Chem. Immunol.* 54:21-43; Clerici, M and Shearer, G. M. (1993) *Immunology Today* 14:107-111; Yamamura, M., et al. (1993) *J Clin. Invest.* 91:1005-1010; Pisa, P., et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:7708-7712; Fauci, A. S. (1988) *Science* 239:617-623).

20 Certain autoimmune diseases have been shown to be associated with a predominant Th1 response. For example, patients with rheumatoid arthritis have predominantly Th1 cells in synovial tissue (Simon, A. K., et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:8562-8566) and experimental autoimmune encephalomyelitis (EAE) can be induced by autoreactive Th1 cells (Kuchroo, V. 25 K., et al. (1993) *J. Immunol.* 151:4371-4381).

The ability to alter or manipulate ratios of Th1 and Th2 subsets requires 30 an understanding of the mechanisms by which the differentiation of CD4 T helper precursor cells (Thp), which secrete only IL-2, choose to become Th1 or Th2 effector cells. It is clear that the cytokines themselves are potent Th cell inducers and form an autoregulatory loop (see e.g., Paul, W. E. and Seder, R. A. (1994) *Cell* 76:241-251; Seder, R. A. and Paul, W. E. (1994) *Ann. Rev. Immunol.* 12:635-673). Thus, IL4 promotes the differentiation of Th2 cells while

preventing the differentiation of precursors into Th1 cells, while IL-12 and IFN- $\gamma$  have the opposite effect.

According to the invention, one way to alter Th1:Th2 ratios is to increase or decrease the level of selected cytokines by using CD83. Direct administration 5 of cytokines or antibodies to cytokines has been shown to have an effect on certain diseases mediated by either Th1 or Th2 cells. For example, administration of recombinant IL-4 or antibodies to IL-12 ameliorate EAE, a Th1-driven autoimmune disease (see Racker; M. K. et al. (1994) J. Exp. Med. 180:1961-1966; and Leonard, J. P. et al. (1995) J. Exp. Med. 181:381-386), 10 while anti-IL-4 antibodies can ameliorate the Th2-mediated parasitic disease, Leishmania major (Sadick, M. D. et al. (1990) J. Exp. Med. 171:115-127).

Numerous disease conditions are associated with either a predominant Th1-type response or a predominant Th2-type response and the individuals suffering from such disease conditions could benefit from treatment with the 15 CD83 related compositions and methods of the invention. Application of the immunomodulatory methods of the invention to such diseases is described in further detail below.

#### *Allergies*

20 Allergies are mediated through IgE antibodies whose production is regulated by the activity of Th2 cells and the cytokines produced thereby. In allergic reactions, IL-4 is produced by Th2 cells, which further stimulates production of IgE antibodies and activation of cells that mediate allergic reactions, i.e., mast cells and basophils. IL-4 also plays an important role in 25 eosinophil mediated inflammatory reactions.

Accordingly, the stimulation of CD83 production by use of the 30 compositions and methods of the invention can be used to inhibit the production of Th2-associated cytokines, for example IL-4, in allergic patients as a means to down-regulate production of pathogenic IgE antibodies. A stimulatory agent may be directly administered to the subject mammal. Alternatively, the CD83 stimulatory agent (e.g. CD83 expression cassette) can be administered to cells (e.g., Thp cells or Th2 cells) that may be obtained from the subject and those modified cells can be readministered to the subject mammal. Moreover, in

certain situations it may be beneficial to co-administer the allergen together with the stimulatory agent either to the subject or to cells treated with the stimulatory agent. Such co-administration can inhibit (e.g., desensitize) the allergen-specific response. The treatment may be further enhanced by administering Th1-promoting agents, such as the cytokine IL-12 or antibodies to Th2-associated cytokines (e.g., anti-IL-4 antibodies), to the allergic subject in amounts sufficient to further stimulate a Th1-type response.

*Cancer*

10       The invention also relates to CD83-related methods for increasing interleukin-10 (IL-10) levels to reduce the spread of neoplastic diseases and/or prevent neoplastic diseases and the growth of a tumor. According to the invention, decreased CD83 activity can dramatically increase the levels of IL-10 in the body and such increased interleukin-10 can be used to treat neoplastic diseases. Hence, the invention provides a method for preventing or treating tumors in a mammal, which involves diminishing CD83 expression or activity in the mammal. In various embodiments, the tumor is IL-2-dependent, a plasmacytoma, or a leukemia, including a lymphocytic leukemia such as a B cell lymphocytic leukemia.

15       The invention also provides methods for increasing T cell activation or T cell proliferation by increasing CD83 activity or expression. Such methods can also be used to prevent or treat tumors in a mammal.

*Infectious Diseases*

20       The expression of Th2-promoting cytokines also has been reported to increase during a variety of infectious diseases. For example, HIV infection, tuberculosis, leishmaniasis, schistosomiasis, filarial nematode infection, intestinal nematode infection and other such infectious diseases are associated with a Th1 to Th2 shift in the immune response. See e.g., Shearer, G. M. and Clerici, M. (1992) Prog. Chem. Immunol. 54:2143; Clerici, M and Shearer, G. M. (1993) Immunology Today 14:107-111; Fauci, A. S. (1988) Science 239:617-623; Locksley, R. M. and Scott, P. (1992) Immunoparasitology Today 1:A58-A61; Pearce, E. J., et al. (1991) J. Exp. Med. 173:159-166; Grzych, J-M., et al.

(1991) *J. Immunol.* 141:1322-1327; Kullberg, M. C., et al. (1992) *J. Immunol.* 148:3264-3270; Bancroft, A. J., et al. (1993) *J. Immunol* 150:1395-1402; Pearlman, E., et al. (1993) *Infect. Immun.* 61:1105-1112; Else, K. J., et al. (1994) *J. Exp. Med.* 179:347-351.

5 Accordingly, the stimulatory CD83-related compositions and methods of the invention can be used to inhibit the production of Th2-cells in subjects with infectious diseases to promote an ongoing Th1 response in the patients and to ameliorate the course of the infection. The treatment may be further enhanced by administering other Th1-promoting agents, such as the cytokine IL-12 or  
10 antibodies to Th2-associated cytokines (e.g., anti-IL-4 antibodies), to the recipient in amounts sufficient to further stimulate a Th 1-type response.

Hence, for example, infections of the following microbial organisms can be treated by the methods of the invention: *Aeromonas* spp., *Bacillus* spp., *Bacteroides* spp., *Campylobacter* spp., *Clostridium* spp., *Enterobacter* spp.,  
15 *Enterococcus* spp., *Escherichia* spp., *Gastospirillum* sp., *Helicobacter* spp., *Klebsiella* spp., *Salmonella* spp., *Shigella* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Vibrio* spp., *Yersinia* spp., and the like. Infections that can be treated by the methods of the invention include those associated with staph infections (*Staphylococcus aureus*), typhus (*Salmonella typhi*), food poisoning  
20 (*Escherichia coli*, such as O157:H7), bacillary dysentery (*Shigella dysenteriae*), pneumonia (*Pseudomonas aeruginosa* and/or *Pseudomonas cepacia*), cholera (*Vibrio cholerae*), ulcers (*Helicobacter pylori*) and others. *E. coli* serotype 0157:H7 has been implicated in the pathogenesis of diarrhea, hemorrhagic colitis, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic  
25 purpura (TTP). The methods of the invention are also active against drug-resistant and multiply-drug resistant strains of bacteria, for example, multiply-resistant strains of *Staphylococcus aureus* and vancomycin-resistant strains of *Enterococcus faecium* and *Enterococcus faecalis*.

The methods of the invention are also effective against viruses. The term  
30 "virus" refers to DNA and RNA viruses, viroids, and prions. Viruses include both enveloped and non-enveloped viruses, for example, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), poxviruses, herpes viruses, adenoviruses, papovaviruses, parvoviruses,

reoviruses, orbiviruses, picornaviruses, rotaviruses, alphaviruses, rubiviruses, influenza virus type A and B, flaviviruses, coronaviruses, paramyxoviruses, morbilliviruses, pneumoviruses, rhabdoviruses, lyssaviruses, orthmyxoviruses, bunyaviruses, phleboviruses, nairoviruses, hepadnaviruses, arenaviruses,  
5 retroviruses, enteroviruses, rhinoviruses and the filovirus.

*Autoimmune Diseases*

The CD83-related compositions and methods of the invention can be used in the treatment of autoimmune diseases that are associated with a Th2-type dysfunction. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against "self tissues" and that promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Modulation of T helper-type responses can have an effect on the course of the autoimmune disease. For example, in experimental allergic encephalomyelitis, stimulation of a Th2-type response by administration of IL-4 at the time of the induction of the disease diminishes the intensity of the autoimmune disease (Paul, W. E., et al. (1994) Cell 76:241-251). Furthermore, recovery of the animals from the disease has been shown to be associated with an increase in a Th2-type response as evidenced by an increase of Th2-specific cytokines (Koury, S. J., et al. (1992) J Exp. Med. 176:1355-1364). Moreover, T cells that can suppress EAE secrete Th2-specific cytokines (Chen, C., et al. (1994) Immunity 1:147-154). Since stimulation of a Th2-type response in experimental allergic encephalomyelitis has a protective effect against the disease, stimulation of a Th2 response in subjects with multiple sclerosis (for which EAE is a model) is likely to be beneficial therapeutically.

Similarly, stimulation of a Th2-type response in type I diabetes in mice provides a protective effect against the disease. Indeed, treatment of NOD mice with IL-4 (which promotes a Th2 response) prevents or delays onset of type I diabetes that normally develops in these mice (Rapoport, M. J., et al. (1993) J. Exp. Med. 178:87-99). Thus, inhibition of CD83 production can stimulate IL-4 production and/or a Th2 response in a subject suffering from or susceptible to diabetes may ameliorate the effects of the disease or inhibit the onset of the disease.

Yet another autoimmune disease in which stimulation of a Th2-type response may be beneficial is rheumatoid arthritis (RA). Studies have shown that patients with rheumatoid arthritis have predominantly Th1 cells in synovial tissue (Simon, A. K., et al., (1994) Proc. Natl. Acad. Sci. USA 91:8562-8566).

5 By stimulating a Th2 response in a subject with rheumatoid arthritis, the detrimental Th1 response can be concomitantly down-modulated to thereby ameliorate the effects of the disease.

Accordingly, the CD83-related compositions and methods of the invention can be used to stimulate production of Th2-associated cytokines in  
10 subjects suffering from, or susceptible to, an autoimmune disease in which a Th2-type response is beneficial to the course of the disease. Such compositions and methods would modulate CD83 activity. In some embodiments, the compositions would decrease CD83 activity and thereby increase the level of certain cytokines, for example, IL-4 levels are increased when CD83 activity is  
15 diminished. The treatment may be further enhanced by administering other Th2-promoting agents, such as IL-4 itself or antibodies to Th1-associated cytokines, to the subject in amounts sufficient to further stimulate a Th2-type response. The treatment may be further enhanced by administering a Th1-promoting cytokine (e.g., IFN- $\gamma$ ) to the subject in amounts sufficient to further stimulate a Th1-type  
20 response.

The efficacy of CD83-related for treating autoimmune diseases can be tested in the animal models provided herein or other models of human diseases (e.g., EAE as a model of multiple sclerosis and the NOD mice as a model for diabetes). Such animal models include the mrl/lpr/lpr mouse as a model for lupus  
25 erythematosus, murine collagen-induced arthritis as a model for rheumatoid arthritis, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856). A CD83-modulatory (i.e., stimulatory or inhibitory) agent of the invention is administered to test animals and the course of the disease in the test animals is then monitored by the  
30 standard methods for the particular model being used. Effectiveness of the modulatory agent is evidenced by amelioration of the disease condition in animals treated with the agent as compared to untreated animals (or animals treated with a control agent).

Non-limiting examples of autoimmune diseases and disorders having an autoimmune component that may be treated according to the invention include diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), multiple sclerosis, myasthenia gravis, 5 systemic lupus erythematosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, 10 asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, 15 polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis.

20           *Transplantation*

While graft rejection or graft acceptance may not be attributable exclusively to the action of a particular T cell subset (i.e., Th1 or Th2 cells) in the graft recipient, studies have implicated a predominant Th2 response in prolonged graft survival and a predominant Th1 response in graft rejection (for a 25 discussion see Dallman, M. J. (1995) Curr. Opin. Immunol. 7:632-638; Takeuchi, T. et al. (1992) Transplantation 53:1281-1291; Tzakis, A. G. et al. (1994) J. Pediatr. Surg. 29:754-756; Thai, N. L. et al. (1995) Transplantation 59:274-281. Additionally, adoptive transfer of cells having a Th2 cytokine phenotype prolongs skin graft survival (Maeda, H. et al. (1994) Int. Immunol. 30 6:855-862) and reduces graft-versus-host disease (Fowler, D. H. et al. (1994) Blood 84:3540-3549; Fowler, D. H. et al. (1994) Prog. Clin. Biol. Res. 389:533-540). Furthermore, administration of IL-4, which promotes Th2 differentiation, prolongs cardiac allograft survival (Levy, A. E. and Alexander, J. W. (1995)

Transplantation 60:405-406), whereas administration of IL-12 in combination with anti-IL-10 antibodies, which promotes Th1 differentiation, enhances skin allograft rejection (Gorczyński, R. M. et al. (1995) Transplantation 60:1337-1341).

5 As provided herein, loss of CD83 function increases interleukin-4 production, which in turn promotes the differentiation of Th2 cells and depresses the differentiation of precursor cells into Th1 cells. Accordingly, methods of the invention that involve decreasing CD83 function can be used to stimulate production of Th2-associated cytokines in transplant recipients to prolong  
10 survival of the graft. These methods can be used both in solid organ transplantation and in bone marrow transplantation (e.g., to inhibit graft-versus-host disease). These methods can involve either direct administration of a CD83 inhibitory agent to the transplant recipient or ex vivo treatment of cells obtained from the subject (e.g., Thp, Th1 cells, B cells, non-lymphoid cells) with an  
15 inhibitory agent followed by readministration of the cells to the subject. The treatment may be further enhanced by administering other Th2-promoting agents, such as IL-4 itself or antibodies to Th1-associated cytokines, to the recipient in amounts sufficient to further stimulate a Th2-type response.

20 **Additional Methods of Using CD83**

In addition to the foregoing disease situations, the modulatory methods of the invention also are useful for other purposes.

For example, inhibition of CD83 activity or function gives rise to increased granulocyte macrophage-colony stimulating factor (GM-CSF).  
25 Granulocyte macrophage colony stimulating factor is a hematopoietic growth factor that promotes the proliferation and differentiation of hematopoietic progenitor cells. GM-CSF is approved for treatment of patients requiring increased proliferation of white blood cells. Data indicates that GM-CSP is also useful as a vaccine adjuvant Morrissey, et al., J. Immunology 139, 1113-1119  
30 (1987). GM-CSF can also be used to treat patients prone to infection such as those undergoing high risk bowel surgery, trauma victims and individuals with HIV.

Accordingly, the invention provides a method of increasing the levels of

GM-CSF in a mammal or in a mammalian cell by administering an agent that modulates or inhibits CD83 activity or expression.

The invention also provides a method of decreasing the levels of GM-CSF in a mammal or in a mammalian cell by administering an agent that modulates or stimulates CD83 activity or expression.

Moreover, in other embodiments the CD83 inhibitory methods of the invention can be used to stimulate production of IL-4 or IL-10 in vitro for commercial production of these cytokines. For example, CD4+ T cells with a null or other mutation in the CD83 gene can be cultured and then stimulated to produce cytokines, for example, by use of anti-CD3 and/or anti-CD28 antibodies to activate the mutant CD4+ T cells. Significant amounts of IL-4 and IL-10 can then be isolated from the culture media. Alternatively, CD4+ T cells can be contacted with the CD83 inhibitory agent in vitro to stimulate IL-4 or IL-10 production and the IL-4 or IL-10 can be recovered from the culture supernatant.

15 The isolated IL-4 and/or IL-10 can be further purified if necessary, and packaged for commercial use.

The methods of the invention can be adapted to vaccinations to promote either a Th1 or a Th2 response to an antigen of interest in a subject. That is, CD83 or CD83 modulators of the invention can serve as adjuvants to direct an immune response to a vaccine either to a Th1 response or a Th2 response. For example, to stimulate an antibody response to an antigen of interest (i.e., for vaccination purposes), the antigen and a CD83 inhibitory agent of the invention can be coadministered to a subject to promote a Th2 response to the antigen in the subject, since Th2 responses provide efficient B cell help and promote IgG1 production.

25 Alternatively, to promote a cellular immune response to an antigen of interest, the antigen and a CD83 stimulating agent of the invention can be coadministered to a subject to promote a Th1 response to the antigen in a subject, since Th1 responses favor the development of cell-mediated immune 30 responses (e.g., delayed hypersensitivity responses).

The antigen of interest and the modulatory agent can be formulated together into a single pharmaceutical composition or in separate compositions.

Thus, in some embodiments, the antigen of interest and the modulatory agent are administered simultaneously to the subject. Alternatively, in certain situations it may be desirable to administer the antigen first and then the modulatory agent or vice versa. For example, in the case of an antigen that naturally evokes a Th1 response, it may be beneficial to first administer the antigen alone to stimulate a Th1 response and then administer a CD83 inhibitory agent, alone or together with a boost of antigen, to shift the immune response to a Th2 response.

According to the invention, any agent that can modulate CD83 to increase or decrease cytokine levels, increase or decrease T cell levels or produce any other CD83-related response can be used in the compositions and methods of the invention. In some embodiments, anti-CD83 antibodies of the invention are used to either activate or inhibit CD83 activity. Activation or inhibition by such antibodies can depend on the epitope to which the antibody binds. Hence, antibodies may play a role in boosting or depressing CD83 activity. These CD83 modulatory agents, including anti-CD83 antibodies, are described in more detail below.

#### Stimulating or Inhibiting CD83

According to the invention, any agent that can stimulate CD83 to perform its natural functions can be used in the compositions and methods of the invention as a CD83 stimulatory agent. Indicators that CD83 activity is stimulated include increased IL-2 cytokine levels, increased T cell levels, and increased TNF levels relative to unstimulated levels in wild type CD83 cells.

Examples of CD83 stimulatory agents include, for example, the CD83 gene product itself, certain anti-CD83 antibodies, CD83-encoding nucleic acids (DNA or RNA), factors that promote CD83 transcription or translation, organic molecules, peptides and the like.

Also, according to the invention, any agent that can inhibit CD83 from performing its natural functions can be used in the compositions and methods of the invention as a CD83 inhibitory agent. Indicators that CD83 activity is inhibited include increased IL-4 cytokine levels, increased IL-10 levels, decreased IL-2

production, decreased T cell levels, and decreased TNF levels relative to uninhibited levels in wild type CD83 cells.

Examples of CD83 inhibitors include anti-CD83 antibodies, CD83 anti-sense nucleic acids (e.g. nucleic acids that can hybridize to CD83 nucleic acids),  
5 organic compounds, peptides and agents that can mutate an endogenous CD83 gene. In some embodiments, the CD83 stimulatory or inhibitory agents are proteins, for example, CD83 gene products, anti-CD83 antibody preparations, CD83 inhibitors, peptides and protein factors that can promote CD83 transcription or translation. In other embodiments, the CD83 stimulatory or  
10 inhibitory agents are peptides or organic molecules. Such proteins, organic molecules and organic molecules can be prepared and/or purified as described herein or by methods available in the art, and administered as provided herein.

In other embodiments, the CD83 stimulatory or inhibitory agents can be nucleic acids including recombinant expression vectors or expression cassettes  
15 encoding CD83 gene products, CD83 transcription factors, CD83 anti-sense nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors. Such nucleic acids can be operably linked to a promoter that is functional in a mammalian cell, and then introduced into cells of the subject mammal using methods known in the art for introducing nucleic acid  
20 (e.g., DNA) into cells.

The "promoter functional in a mammalian cell" or "mammalian promoter" is capable of directing transcription of a polypeptide coding sequence operably linked to the promoter. The promoter should generally be active in T cells and antigen presenting cells and may be obtained from a gene that is  
25 expressed in T cells or antigen presenting cells. However, it need not be a T cell-specific or an antigen presenting cell specific-promoter. Instead, the promoter may be selected from any mammalian or viral promoter that can function in a T cell. Hence the promoter may be an actin promoter, an immunoglobulin promoter, a heat-shock promoter, or a viral promoter obtained  
30 from the genome of viruses such as adenoviruses, retroviruses, lentiviruses, herpes viruses, including but not limited to, polyoma virus, fowlpox virus, adenovirus 2, bovine papilloma virus, avian sarcoma virus, cytomegalovirus (CMV), hepatitis-B virus, Simian Virus 40 (SV40), Epstein Barr virus (EBV),

feline immunodeficiency virus (FIV), and SV40, or are respiratory syncytial viral promoters (RSV) or long terminal repeats (LTRs) of a retrovirus, i.e., a Moloney Murine Leukemia Virus (MoMuLV) (Cepko et al. (1984) Cell 37:1053-1062). The promoter functional in a mammalian cell can be inducible or 5 constitutive.

Any cloning procedure used by one of skill in the art can be employed to make the expression vectors or expression that comprise a promoter operably linked to a CD83 nucleic acid, CD83 transcription factor or a nucleic acid encoding an anti-CD83 antibody. See, e.g., Sambrook et al., Molecular Cloning, 10 A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 1989; Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 2001.

After constructing an expression vector or an expression cassette encoding CD83 gene products, CD83 transcription factors, CD83 anti-sense 15 nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors, mammalian cells can be transformed with the vector or cassette. Examples of such methods include:

*Direct Injection:* Naked DNA can be introduced into cells in vivo by directly injecting the DNA into the cells (see e.g., Acsadi et al. (1991) Nature 20 332:815-818; Wolff et al. (1990) Science 247:1465-1468). For example, a delivery apparatus (e.g., a "gene gun") for injecting DNA into cells in vivo can be used. Such an apparatus is commercially available (e.g., from BioRad).

*Receptor-Mediated DNA Uptake:* Naked DNA can also be introduced into cells in vivo by complexing the DNA to a cation, such as polylysine, which 25 is coupled to a ligand for a cell-surface receptor (see for example Wu, G. and Wu, C. H. (1988) J. Biol. Chem. 263:14621; Wilson et al. (1992) J. Biol. Chem. 267:963-967; and U.S. Pat. No. 5,166,320). Binding of the DNA-ligand 30 complex to the receptor facilitates uptake of the DNA by receptor-mediated endocytosis. A DNA-ligand complex linked to adenovirus capsids that naturally disrupt endosomes, thereby releasing material into the cytoplasm can be used to avoid degradation of the complex by intracellular lysosomes (see for example Curiel et al. (1991) Proc. Natl. Acad. Sci. USA 88:8850; Cristiano et al. (1993) Proc. Natl. Acad. Sci. USA 90:2122-2126).

*Retroviruses:* Defective retroviruses are well characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A. D. (1990) Blood 76:271). A recombinant retrovirus can be constructed having nucleotide sequences of interest incorporated into the retroviral genome. Additionally, 5 portions of the retroviral genome can be removed to render the retrovirus replication defective. The replication defective retrovirus is then packaged into virions that can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current 10 Protocols in Molecular Biology, Ausubel, F. M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals. Examples of suitable retroviruses include pLJ, pZIP, pWE and pEM which are available to those skilled in the art. Examples of suitable packaging virus lines include  $\Psi$ Crip,  $\Psi$ Cre,  $\Psi$ 2 and  $\Psi$ Am. Retroviruses have been used to introduce a 15 variety of genes into many different cell types, including epithelial cells, endothelial cells, lymphocytes, myoblasts, hepatocytes, bone marrow cells, *in vitro* and/or *in vivo* (see for example Eglitis, et al. (1985) Science 230:1395-1398; Danos and Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:6460-6464; Wilson et al. (1988) Proc. Natl. Acad. Sci. USA 85:3014-3018; Armentano et al. 20 (1990) Proc. Natl. Acad. Sci. USA 87:6141-6145; Huber et al. (1991) Proc. Natl. Acad. Sci. USA 88:8039-8043; Ferry et al. (1991) Proc. Natl. Acad. Sci. USA 88:8377-8381; Chowdhury et al. (1991) Science 254:1802-1805; van Beusechem et al. (1992) Proc. Natl. Acad. Sci. USA 89:7640-7644; Kay et al. (1992) Human Gene Therapy 3:641-647; Dai et al. (1992) Proc. Natl. Acad. Sci. USA 89:10892-25 10895; Hwu et al. (1993) J. Immunol. 150:4104-4115; U.S. Pat. Nos. 4,868,116; 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573). Retroviral vectors require target cell division in order for the retroviral genome (and foreign nucleic acid inserted into it) to be integrated into the host genome to 30 stably introduce nucleic acid into the cell. Thus, it may be necessary to stimulate replication of the target cell.

*Adenoviruses:* The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms

of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner et al. (1988) BioTechniques 6:616; Rosenfeld et al. (1991) Science 252:431-434; and Rosenfeld et al. (1992) Cell 68:143-155. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of 5 adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are available to those skilled in the art. Recombinant adenoviruses are advantageous in that they do not require dividing cells to be effective gene delivery vehicles and can be used to infect a wide variety of cell types, including airway epithelium (Rosenfeld et al. (1992) cited supra), endothelial cells (Lemarchand et al. (1992) Proc. Natl. Acad. Sci. USA 10 89:6482-6486), hepatocytes (Herz and Gerard (1993) Proc. Natl. Acad. Sci. USA 90:2812-2816) and muscle cells (Quantin et al. (1992) Proc. Natl. Acad. Sci. USA 89:2581-2584). Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result 15 of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (e.g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner et al. cited supra; Haj-Ahmad and Graham (1986) J. Virol. 57:267). Most replication-defective adenoviral 20 vectors currently in use are deleted for all or parts of the viral E1 and E3 genes but retain as much as 80% of the adenoviral genetic material.

*Adeno-Associated Viruses:* Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. 25 (For a review see Muzyczka et al. Curr. Topics in Micro. and Immunol. (1992) 158:97-129). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte et al. (1992) Am. J. Respir. Cell. Mol. Biol. 7:349-356; Samulski et al. (1989) J. Virol. 63:3822-3828; and McLaughlin et al. (1989) J. Virol. 30 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al. (1985) Mol. Cell. Biol. 5:3251-3260 can be used to introduce DNA into cells. A variety of nucleic

acids have been introduced into different cell types using AAV vectors (see for example Hermonat et al. (1984) Proc. Natl. Acad. Sci. USA 81:6466-6470; Tratschin et al. (1985) Mol. Cell. Biol. 4:2072-2081; Wondisford et al. (1988) Mol. Endocrinol. 2:32-39; Tratschin et al. (1984) J Virol. 51:611-619; and Flotte et al. (1993) J. Biol. Chem. 268:3781-3790).

Transformed mammalian cells can then be identified and administered to the mammal from whence they came to permit expression of a CD83 gene product, CD83 transcription factor, CD83 anti-sense nucleic acid, intracellular antibody capable of binding to CD83 proteins, or dominant negative CD83 inhibitors. The efficacy of a particular expression vector system and method of introducing nucleic acid into a cell can be assessed by standard approaches routinely used in the art. For example, DNA introduced into a cell can be detected by a filter hybridization technique (e.g., Southern blotting). RNA produced by transcription of an introduced DNA can be detected, for example, by Northern blotting, RNase protection or reverse transcriptase-polymerase chain reaction (RT-PCR). The CD83 gene product can be detected by an appropriate assay, for example, by immunological detection of a produced CD83 protein, such as with a CD83-specific antibody.

## 20 CD83 Antibodies

The invention provides antibody preparations directed against the mutant and wild type CD83 polypeptides of the invention, for example, against a polypeptide having SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9. Other antibodies of interest can bind to the cytoplasmic tail of 25 CD83.

In one embodiment, the invention provides antibodies that block the function of CD83 polypeptides. Such antibodies may be used as CD83 inhibitory agents in the methods of the invention as described herein. In another embodiment, the antibodies of the invention can activate CD83 activity. Such 30 activating antibodies may be used as CD83 stimulatory agents.

All antibody molecules belong to a family of plasma proteins called immunoglobulins, whose basic building block, the immunoglobulin fold or domain, is used in various forms in many molecules of the immune system and

other biological recognition systems. A typical immunoglobulin has four polypeptide chains, containing an antigen binding region known as a variable region and a non-varying region known as the constant region.

Native antibodies and immunoglobulins are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains (Clothia et al., J. Mol. Biol. 186, 651-66, 1985); Novotny and Haber, Proc. Natl. Acad. Sci. USA 82, 4592-4596 (1985).

Depending on the amino acid sequences of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are at least five (5) major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG-1, IgG-2, IgG-3 and IgG-4; IgA-1 and IgA-2. The heavy chains constant domains that correspond to the different classes of immunoglobulins are called alpha ( $\alpha$ ), delta ( $\delta$ ), epsilon ( $\epsilon$ ), gamma ( $\gamma$ ) and mu ( $\mu$ ), respectively. The light chains of antibodies can be assigned to one of two clearly distinct types, called kappa ( $\kappa$ ) and lambda ( $\lambda$ ), based on the amino sequences of their constant domain. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "variable" in the context of variable domain of antibodies, refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies. The variable domains are for binding and determine the specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed through the variable domains

of antibodies. It is concentrated in three segments called complementarity determining regions (CDRs) also known as hypervariable regions both in the light chain and the heavy chain variable domains.

The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a  $\beta$ -sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the  $\beta$ -sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector function, such as participation of the antibody in antibody-dependent cellular toxicity.

An antibody that is contemplated for use in the present invention thus can be in any of a variety of forms, including a whole immunoglobulin, an antibody fragment such as Fv, Fab, and similar fragments, a single chain antibody that includes the variable domain complementarity determining regions (CDR), and the like forms, all of which fall under the broad term "antibody," as used herein. The present invention contemplates the use of any specificity of an antibody, polyclonal or monoclonal, and is not limited to antibodies that recognize and immunoreact with a specific antigen. In preferred embodiments, in the context of both the therapeutic and screening methods described below, an antibody or fragment thereof is used that is immunospecific for an antigen or epitope of the invention.

The term "antibody fragment" refers to a portion of a full-length antibody, generally the antigen binding or variable region. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub> and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an F(ab')<sub>2</sub> fragment that has two antigen binding fragments, which are capable of cross-linking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody

molecules, and multispecific antibodies formed from antibody fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and F(ab')<sub>2</sub> fragments.

Antibody fragments retain some ability to selectively bind with its 5 antigen or receptor and are defined as follows:

(1) Fab is the fragment that contains a monovalent antigen-binding fragment of an antibody molecule. A Fab fragment can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain.

10 (2) Fab' is the fragment of an antibody molecule can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per antibody molecule. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain 15 including one or more cysteines from the antibody hinge region.

(3) (Fab')<sub>2</sub> is the fragment of an antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction. F(ab')<sub>2</sub> is a dimer of two Fab' fragments held together by two disulfide bonds.

20 (4) Fv is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (V<sub>H</sub>-V<sub>L</sub> dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V<sub>H</sub>-V<sub>L</sub> dimer. Collectively, the six CDRs confer antigen binding specificity to the 25 antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

(5) Single chain antibody ("SCA"), defined as a genetically engineered molecule containing the variable region of the light chain, the 30 variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Such single chain antibodies are also referred to as "single-chain Fv" or "sFv" antibody fragments. Generally, the Fv polypeptide further comprises a polypeptide linker between the VH and VL

domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds. Springer-Verlag, N.Y., pp. 269-315 (1994).

5 The term "diabodies" refers to a small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the  
10 complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161, and Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993).

The preparation of polyclonal antibodies is well-known to those skilled in the art. See, for example, Green, et al., *Production of Polyclonal Antisera*, in:  
15 Immunochemical Protocols (Manson, ed.), pages 1-5 (Humana Press); Coligan, et al., *Production of Polyclonal Antisera in Rabbits, Rats Mice and Hamsters*, in: Current Protocols in Immunology, section 2.4.1 (1992), which are hereby incorporated by reference.

The preparation of monoclonal antibodies likewise is conventional. See,  
20 for example, Kohler & Milstein, *Nature*, 256:495 (1975); Coligan, et al., sections 2.5.1-2.6.7; and Harlow, et al., in: Antibodies: A Laboratory Manual, page 726 (Cold Spring Harbor Pub. (1988)), which are hereby incorporated by reference. Methods of *in vitro* and *in vivo* manipulation of monoclonal antibodies are also available to those skilled in the art. For example, the monoclonal antibodies to  
25 be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, *Nature* 256, 495 (1975), or may be made by recombinant methods, e.g., as described in U.S. Patent No. 4,816,567. The monoclonal antibodies for use with the present invention may also be isolated from antibody libraries using the techniques described in  
30 Clackson et al. *Nature* 352: 624-628 (1991), as well as in Marks et al., *J. Mol Biol.* 222: 581-597 (1991).

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques

include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, e.g., Coligan, et al., sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; Barnes, et al., Purification of Immunoglobulin G (IgG), in: Methods in Molecular Biology, Vol. 10, pages 79-5 104 (Humana Press (1992)).

Another method for generating antibodies involves a Selected Lymphocyte Antibody Method (SLAM). The SLAM technology permits the generation, isolation and manipulation of monoclonal antibodies without the process of hybridoma generation. The methodology principally involves the 10 growth of antibody forming cells, the physical selection of specifically selected antibody forming cells, the isolation of the genes encoding the antibody and the subsequent cloning and expression of those genes.

More specifically, an animal (rabbit, mouse, rat, other) is immunized with a source of specific antigen. This immunization may consist of purified 15 protein, in either native or recombinant form, peptides, DNA encoding the protein of interest or cells expressing the protein of interest. After a suitable period, during which antibodies can be detected in the serum of the animal (usually weeks to months), blood (or other tissue) from the animal is harvested. Lymphocytes are isolated from the blood and cultured under specific conditions 20 to generate antibody-forming cells, with antibody being secreted into the culture medium. These cells are detected by any of several means (complement mediated lysis of antigen-bearing cells, fluorescence detection or other) and then isolated using micromanipulation technology. The individual antibody forming cells are then processed for eventual single cell PCR to obtain the expressed 25 Heavy and Light chain genes that encode the specific antibody. Once obtained and sequenced, these genes are cloned into an appropriate expression vector and recombinant, monoclonal antibody produced in a heterologous cell system. These antibodies are then purified via standard methodologies such as the use of protein A affinity columns. These types of methods are further described in 30 Babcock, et al., Proc. Natl. Acad. Sci. (USA) 93: 7843-7848 (1996); U.S. Patent No. 5,627,052; and PCT WO 92/02551 by Schrader.

Another method involves humanizing a monoclonal antibody by recombinant means to generate antibodies containing human specific and

recognizable sequences. See, for review, Holmes, et al., *J. Immunol.*, 158:2192-2201 (1997) and Vaswani, et al., *Annals Allergy, Asthma & Immunol.*, 81:105-115 (1998). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies,

5 i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional polyclonal antibody preparations that typically include different antibodies directed against different

10 determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the antibody is obtained from a substantially homogeneous population

15 of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies

20 derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567);

25 Morrison et al. *Proc. Natl. Acad Sci.* 81, 6851-6855 (1984).

Methods of making antibody fragments are also known in the art (see for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, (1988), incorporated herein by reference). Antibody fragments of the present invention can be prepared by proteolytic

30 hydrolysis of the antibody or by expression in *E. coli* of DNA encoding the fragment. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S

fragment denoted F(ab')<sub>2</sub>. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulphydryl groups resulting from cleavage of disulfide linkages, to produce 3.5S Fab= monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two 5 monovalent Fab' fragments and an Fc fragment directly. These methods are described, for example, in U.S. Patents No. 4,036,945 and No. 4,331,647, and references contained therein. These patents are hereby incorporated in their entireties by reference.

Other methods of cleaving antibodies, such as separation of heavy chains 10 to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody. For example, Fv fragments comprise an association of V<sub>H</sub> and V<sub>L</sub> chains. This association may be noncovalent or the variable chains can be linked by an 15 intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. Preferably, the Fv fragments comprise V<sub>H</sub> and V<sub>L</sub> chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V<sub>H</sub> and V<sub>L</sub> domains connected by an oligonucleotide. The 20 structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as *E. coli*. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing sFvs are described, for example, by Whitlow, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 97 (1991); 25 Bird, et al., Science 242:423-426 (1988); Ladner, et al., US Patent No. 4,946,778; and Pack, et al., Bio/Technology 11:1271-77 (1993).

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal 30 recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 106 (1991).

The invention further contemplates human and humanized forms of non-human (e.g. murine) antibodies. Such humanized antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a nonhuman species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity.

In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, humanized antibodies can comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the Fv regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see: Jones et al., Nature 321, 522-525 (1986); Reichmann et al., Nature 332, 323-329 (1988); Presta, Curr. Op. Struct. Biol. 2, 593-596 (1992); Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998).

The invention also provides methods of mutating antibodies to optimize their affinity, selectivity, binding strength or other desirable property. A mutant antibody refers to an amino acid sequence variant of an antibody. In general, one or more of the amino acid residues in the mutant antibody is different from what is present in the reference antibody. Such mutant antibodies necessarily have less than 100% sequence identity or similarity with the reference amino acid sequence. In general, mutant antibodies have at least 75% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody. Preferably, mutant antibodies

have at least 80%, more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody.

5       The antibodies of the invention are isolated antibodies. An isolated antibody is one that has been identified and separated and/or recovered from a component of the environment in which it was produced. Contaminant components of its production environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, 10 hormones, and other proteinaceous or nonproteinaceous solutes. The term "isolated antibody" also includes antibodies within recombinant cells because at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

15      If desired, the antibodies of the invention can be purified by any available procedure. For example, the antibodies can be affinity purified by binding an antibody preparation to a solid support to which the antigen used to raise the antibodies is bound. After washing off contaminants, the antibody can be eluted by known procedures. Those of skill in the art will know of various techniques 20 common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (see for example, Coligan, et al., Unit 9, Current Protocols in Immunology, Wiley Interscience, 1991, incorporated by reference).

In preferred embodiments, the antibody will be purified as measurable by 25 at least three different methods: 1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; 2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator; or 3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using 30 Coomassie blue or, preferably, silver stain.

The invention also provides antibodies that can bind to CD83 polypeptides. Sequences of complementarity determining regions (CDRs) or hypervariable regions from light and heavy chains of these anti-CD83 antibodies

are provided. For example, a heavy chain variable region having a CDR1 sequence of SYDMT (SEQ ID NO:23), SYDMS (SEQ ID NO:24), DYDLS (SEQ ID NO:25) or SYDMS (SEQ ID NO:26) can be used in an antibody or other binding moiety to bind to CD83 gene products. In other embodiments, a 5 heavy chain variable region having a CDR2 sequence of YASGSTYY (SEQ ID NO:27), SSSGTTYY (SEQ ID NO:28), YASGSTYY (SEQ ID NO:29), AIDGNPYY (SEQ ID NO:30) or STAYNSHY (SEQ ID NO:31) can be used in an antibody or other binding moiety to bind to CD83 gene products. In further 10 embodiments of the invention, a heavy chain variable region having a CDR3 sequence of EHAGYSGDTGH (SEQ ID NO:32), EGAGVSMT (SEQ ID NO:33), EDAGFSNA (SEQ ID NO:34), GAGD (SEQ ID NO:35) or GGSWLD (SEQ ID NO:36) can be used in an antibody or other binding moiety to bind to 15 CD83 gene products.

Moreover, a light chain variable region having a CDR1 sequence of 15 RCAYD (SEQ ID NO:37), RCADVV (SEQ ID NO:38), or RCALV (SEQ ID NO:39) can be used in an antibody or other binding moiety to bind to CD83 gene products. In other embodiments, a light chain variable region having a CDR2 sequence of QSISTY (SEQ ID NO:40), QSVSSY (SEQ ID NO:41), ESISNY (SEQ ID NO:42), KNVYNNNW (SEQ ID NO:43), or QSVYDNDE (SEQ ID 20 NO:43) can be used in an antibody or other binding moiety to bind to CD83 gene products. In further embodiments, a light chain variable region having a CDR3 sequence of QQGYTHSNVDNV (SEQ ID NO:44), QQGYSISIDDNA (SEQ ID NO:45), QCTSGGKFISDGAA (SEQ ID NO:46), AGDYSSSSDNG (SEQ ID NO:47), or QATHYSSDWLTY (SEQ ID NO:48) can be used in an antibody or 25 other binding moiety to bind to CD83 gene products.

Light and heavy chains that can bind CD83 polypeptides are also provided by the invention. For example, in one embodiment, the invention provides a 20D04 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 light chain is provided below (SEQ ID NO:11).

30  
1 MDMRAPTQLL GLLLLWLPGA RCADVVMQT PAVSAAVGG  
41 TVTINCQASE SISNYLSWYQ QKPGQPPKLL IYRTSTLASG  
81 VSSRFKGSGS GTEYTLTISG VQCDDVATYY CQCTSGGKFI  
121 SDGAAFGGGT EVVVKGDPVA PTVLLFPPSS DEVATGTVTI  
35 161 VCVANKYFPD VTWTWEVDGT TQTTGIENSK TPQNSADCTY

201 NLSSTLTLTS TQYN SHKEYT CKVT QGTT SV VQSFSRKNC

A nucleic acid sequence for this 20D04 anti-CD83 light chain is provided below (SEQ ID NO:12).

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5      1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
     41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ATGTCGTGAT
     81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
    121 ACAGTCACCA TCAATTGCCA GGCCAGTGAA AGCATTAGCA
    161 ACTACTTATC CTGGTATCAG CAGAAACCAG GGCAGCCTCC
10     201 CAAGCTCCTG ATCTACAGGA CATCCACTCT GGCATCTGGG
    241 GTCTCATCGC GGITCAAAGG CAGTGGATCT GGGACAGAGT
    281 ACACTCTCAC CATCAGCGGC GTGCAGTGTG ACGATGTTGC
    321 CACTTACTAC TGTCAATGCA CTTCTGGTGG GAAGTTCATT
    361 AGTGATGGTG CTGCTTCCGG CGGAGGGACC GAGGTGGTGG
15     401 TCAAAGGTGA TCCAGTTGCA CCTACTGTCC TCCTCTTCCC
    441 ACCATCTAGC GATGAGGTGG CAACTGGAAC AGTCACCATC
    481 GTGTGTGTGG CGAATAAATA CTTTCCCGAT GTCACCGTCA
    521 CCTGGGAGGT GGATGGCACC ACCCAAACAA CTGGCATCGA
    561 GAACAGTAAA ACACCGCAGA ATTCTGCAGA TTGTACCTAC
20     601 AACCTCAGCA GCACTCTGAC ACTGACCAGC ACACAGTACA
    641 ACAGCCACAA AGAGTACACC TGCAAGGTGA CCCAGGGCAC
    681 GACCTCAGTC GTCCAGAGCT TCAGTAGGAA GAACTGTTAA

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25 In another embodiment, the invention provides a 20D04 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 heavy chain is provided below (SEQ ID NO:13).

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1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
30    41 TVSGFSL SNN AINWVRQAPG KGLEWIGYIW SGGLTYYANW
    81 AEGRFTISKT STIVDLKMTS PTIEDTATYF CARGINNSAL
    121 WGPGLTVTVS SGQPKAPS VF PLAPCCGDTP SSTVTLGCLV
    161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
    201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
35    241 LLGGPSVFIF PPKPKDTLM I SRTPEVTCVV DVVSQDDPEV
    281 QFTWYINNEQ VRTARPPLRE QQFNSTIRVV STLPIAHQDW
    321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
    361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
    401 TPAVLDS DGS YFLYNKLSVP TSEWQRGDVF TCSV MHEALH
40    441 NHYTQKSISR SPGK

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A nucleic acid sequence for this 20D04 anti-CD83 heavy chain is provided below (SEQ ID NO:14).

1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC  
5 41 TCAAAGGTGT CCAGTGTCAAG TCGGTGGAGG AGTCCGGGG  
81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC  
121 ACCGTCTCTG GATTCTCCCT CAGTAACAAT GCAATAAACT  
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTAG AGTGGATCGG  
201 ATACATTGG AGTGGTGGGC TTACATACTA CGCGAAGTGG  
10 241 GCGGAAGGCC GATTCAACCAT CTCCAAAACC TCGACTACGG  
281 TGGATCTGAA GATGACCAAGT CCGACAATCG AGGACACGGC  
321 CACCTATTTG TGTCAGAG GGATTAATAA CTCCGCTTTG  
361 TGGGGCCAG GCACCCCTGGT CACCGTCTCC TCAGGGCAAC  
401 CTAAGGCTCC ATCAGTCTTC CCACGGCCC CCTGCTGCAG  
15 441 GGACACACCC TCTAGCACGG TGACCTGGG CTGCCTGGTC  
481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAAC  
521 CGGGCACCC CACCAATGGG GTACGCACCT TCCCCTCCGT  
561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG  
601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG  
20 641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC  
681 GCCCTCGACA TGCAGCAAGC CCACGTGCC ACCCCCTGAA  
721 CTCCTGGGG GACCGTCTGT CTTCATCTTC CCCCCAAAC  
761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC  
801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCCGAGGTG  
25 841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG  
881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT  
921 CCGCGTGGTC AGCACCCCTCC CCATCGCGCA CCAGGACTGG  
961 CTGAGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG  
1001 CACTCCCGC CCCCATCGAG AAAACCACCT CCAAAGCCAG  
30 1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT  
1081 CCCCCGGAGG AGCTGAGCAG CAGGTGGTC AGCCTGACCT  
1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA  
1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC  
1201 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT  
35 1241 ACAACAAGCT CTCAGTGCCA ACGAGTGAGT GGCAGCGGG  
1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGCAC

1321 AACCAC TACA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA  
 1361 AA

In another embodiment, the invention provides a 11G05 light chain that  
 5 can bind to CD83 polypeptides. The amino acid sequence for this 11G05 light  
 chain is provided below (SEQ ID NO:15).

1 MDTRAP TQLL GLLLWLPGA RCADVVMTQT PASVSAAVGG  
 41 TVTINCQSSK NVYNNNWLSW FQQKPGQPPK LLIYYASTLA  
 10 81 SGVPSRFRGS GSGTQFTLTI SDVQCDDAAT YYCAGDYSSS  
 121 SDNGFGGGTE VVVKGDPVAP TVLLFPSSD EVATGTVTIV  
 161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN  
 201 LSSTLT LTST QYNSHKEYTC KVTQGITSVV QSFSRKNC

15 A nucleic acid sequence for this 11G05 anti-CD83 light chain is provided  
 below (SEQ ID NO:16).

1 ATGGACACCA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC  
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ACGTCGTGAT  
 81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC  
 20 121 ACAGTCACCA TCAATTGCCA GTCCAGTAAG AATGTTTATA  
 161 ATAACA ACTG GTTATCCTGG TTT CAGCAGA AACCAGGGCA  
 201 GCCTCCCAAG CTCTGATCT ATTATGCATC CACTCTGGCA  
 241 TCTGGGGTCC CATCGCGGTT CAGAGGCAGT GGATCTGGGA  
 281 CACAGTTCAC TCTCACCATT AGCGACGTGC AGTGTGACGA  
 25 321 TGCTGCCACT TACTACTGTG CAGGGCGATTA TAGTAGTAGT  
 361 AGTGATAATG GTTTCGGCGG AGGGACCGAG GTGGTGGTCA  
 401 AAGGTGATCC AGTTGCACCT ACTGTCTCC TCTTCCCACC  
 441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG  
 481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTACACT  
 30 521 GGGAGGTGGA TGGCACCACC CAAACAACTG GCATCGAGAA  
 561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC  
 601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA  
 641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACCGAC  
 681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA

35

In another embodiment, the invention provides a 11G05 heavy chain that  
 can bind to CD83 polypeptides. The amino acid sequence for this 11G05 heavy  
 chain is provided below (SEQ ID NO:17).

40 1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC  
 41 TVSGFTISDY DLSWVRQAPG EGLKYIGFIA IDGNPYYATW

81 AKGRFTISKI STTVDLKITA PTTEDTATYF CARGAGDLWG  
 121 PGTLVTVSSG QPKAPSIVFPL APCCGDPSS TVTLGCLVKG  
 161 YLPEPVTVTW NSGTLTNGVR TFPSVRQSSG LYSLSSVVSV  
 201 TSSSQPVTCN VAHPATNTKV DKTVAPSTCS KPTCPPPELL  
 5 241 GGPSVFIFPP KPKDTLMISR TPEVTCVVVD VSQDDPEVQF  
 281 TWYINNEQVR TARPPLREQQ FNSTIRVVST LPIAHQDWLR  
 321 GKEFKCKVHN KALPAPIEKT ISKARGQPLE PKVYTMGPPR  
 361 EELSSRSVSL TCMINGFYPS DISVEWEKNG KAEDNYKTTP  
 401 AVLDSDGSYF LYNKLSVPTS EWQRGDVFTC SVMHEALHNH  
 10 441 YTQKSISRSP GK

A nucleic acid sequence for this 11G05 anti-CD83 heavy chain is provided below (SEQ ID NO:18).

15 1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC  
 41 41 TCAAAGGTGT CCAGTGTCAAG TCGGTGGAGG AGTCCGGGG  
 81 81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC  
 121 121 ACAGTCTCTG GATTCAACCAT CAGTGACTAC GACTTGAGCT  
 161 161 GGGTCCGCCA GGCTCCAGGG GAGGGGCTGA AATACATCGG  
 20 201 ATTCAATTGCT ATTGATGGTA ACCCATACTA CGCGACCTGG  
 241 241 GCAAAAGGCC GATTCAACCAT CTCCAAAACC TCGACCACGG  
 281 281 TGGATCTGAA AATCACCGCT CCGACAACCG AAGACACGGC  
 321 321 CACGTATTTC TGTGCCAGAG GGGCAGGGGA CCTCTGGGC  
 361 361 CCAGGGACCC TCGTCACCGT CTCTTCAGGG CAACCTAAGG  
 25 401 401 CTCCATCAGT CTTCCCCACTG GCCCCCTGCT GCAGGGACAC  
 441 441 ACCCTCTAGC ACGGTGACCT TGCGCTGCCT GGTCAAAGGC  
 481 481 TACCTCCCGG AGCCAGTGAC CGTGACCTGG AACTCGGCA  
 521 521 CCCTCACCAA TGGGGTACGC ACCTTCCCCT CCGTCCGGCA  
 561 561 GTCCTCAGGC CTCTACTCGC TGAGCAGCGT GGTGAGCGTG  
 30 601 601 ACCTCAAGCA GCCAGCCCGT CACCTGCAAC GTGGCCCACC  
 641 641 CAGCCACCAA CACCAAAGTG GACAAGACCG TTGCGCCCTC  
 681 681 GACATGCAGC AAGCCCACGT GCCCACCCCC TGAACTCCTG  
 721 721 GGGGGACCGT CTGTCTTCAT CTTCCCCCCC AAACCCAAGG  
 761 761 ACACCCCTCAT GATCTCACGC ACCCCCCGAGG TCACATGCCTG  
 35 801 801 GGTGGTGGAC GTGAGGCCAGG ATGACCCCGA GGTGCAGTTC  
 841 841 ACATGGTACA TAAACAACGA GCAGGTGCGC ACCGCCCCGGC

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881 CGCCGCTACG GGAGCAGCAG TTCAACAGCA CGATCCCGT
921 GGTCAAGCACC CTCCCCATCG CGCACCCAGGA CTGGCTGAGG
961 GGCAAGGAGT TCAAGTGCAA AGTCCACAAC AAGGCACCTCC
1001 CGGCCCAT CGAGAAAACC ATCTCCAAAG CCAGAGGGCA
5 1041 GCCCCTGGAG CCGAAGGTCT ACACCATGGG CCCTCCCCGG
1081 GAGGAGCTGA GCAGCAGGTC GGTCAAGCCTG ACCTGCATGA
1120 TCAACGGCTT CTACCCCTCC GACATCTCGG TGGAGTGGGA
1161 GAAGAACGGG AAGGCAGAGG ACAACTACAA GACCACGCCG
1201 GCCGTGCTGG ACAGCGACGG CTCCTACTTC CTCTACAACA
10 1241 AGCTCTCAGT GCCCACGAGT GAGTGGCAGC GGGGCGACGT
1281 CTTCACCTGC TCCGTGATGC ACGAGGCCTT GCACAAACCAC
1321 TACACGCAGA AGTCCATCTC CCGCTCTCCG GGTAAA

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In another embodiment, the invention provides a 14C12 light chain that  
15 can bind to CD83 polypeptides. The amino acid sequence for this 14C12 light  
chain is provided below (SEQ ID NO:19).

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1 MDXRAPPTQLL GLLLLWLPGA RCALVMTQTP ASVSAAVGGT
41 VTINCQSSQS VYDNDELSWY QQKPGQPPKL LIYLASKLAS
20 81 GVPSRFKGSG SGTQFALTIS GVQCDAAATY YCQATHYSSD
121 WYLTFGGGTE VVVKGDPVAP TVLLFPPSSD EVATGTVTIV
161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
201 LSSTLTLTST QYN SHKEYTC KVTQGITSVV QSFSRKNC

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25 A nucleic acid sequence for this 14C12 anti-CD83 light chain is provided  
below (SEQ ID NO:20).

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1 ATGGACATRA GGGCCCCCAC TCAGCTGCTG GGGCTCCCTGC
41 TGCTCTGGCT CCCAGGTGCC AGATGTGCC TTGTGATGAC
30 81 CCAGACTCCA GCCTCCGTGT CTGCAGCTGT GGGAGGCACA
121 GTCACCCTCA ATTGCCAGTC CAGTCAGAGT GTTTATGATA
161 ACGACGAATT ATCCTGGTAT CAGCAGAAAC CAGGGCAGCC
201 TCCCAGCTC CTGATCTATC TGGCATCCAA GTTGGCCTCT
241 GGGGTCCCCAT CCCGATTCAA AGGCAGTGGA TCTGGGACAC
35 281 AGTCGCTCT CACCATCAGC GGCAGTCAGT GTGACGATGC
321 TGCCACTTAC TACTGTCAAG CCACTCATTA TAGTAGTGAT
361 TGGTATCTTA CTTTCGGCGG AGGGACCGAG GTGGTGGTCA
401 AAGGTGATCC AGTTGCACCT ACTGTCTCC TCTTCCCACC
441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
40 481 TGTGTGGCGA ATAAATACCT TCCCGATGTC ACCGTCACCT
521 GGGAGGTGGA TGGCACCACC CAAACAACTG GCATCGAGAA
561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC

```

601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA  
 641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC  
 681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA

5

In another embodiment, the invention provides a 14C12 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 14C12 heavy chain is provided below (SEQ ID NO:21).

	1	METGLRWLLL VAVLKGVHCQ SVEESGGRLV TPGTPLTLTC
10	41	TASGFSRSSY DMSWVRQAPG KGLEWVGVIS TAYNSHYASW
	81	AKGRFTISRT STTVDLKMTS LTTEDDTATYF CARGGSWLDL
	121	WGQGTLVTVS SGQPKAPSVF PLAPCCGDTP SSTVTLGCLV
	161	KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
	201	SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
15	241	LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDVSQDDPEV
	281	QFTWYINNEQ VRTARPPLRE QQFNSTIRVV STLPIAHQDW
	321	LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
	361	PREEELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
20	401	TPAVLSDSDGS YFLYNKLSVP TSEWQRGDVF TCSVHEALH
	441	NHYTQKSISR SPGK

A nucleic acid sequence for this 14C12 anti-CD83 heavy chain is provided below (SEQ ID NO:22).

25	1	ATGGAGACAG GCCTGCGCTG GCITTCTCCTG GTCGCTGTGC
	41	TCAAAGGTGT CCACTGTCAG TCGGTGGAGG AGTCCGGGGG
	81	TCGCCTGGTC ACCGCCTGGGA CACCCCTGAC ACTCACCTGC
	121	ACAGCCTCTG GATTCTCCCG CAGCAGCTAC GACATGAGCT
	161	GGGTCCGCCA GGCTCCAGGG AAGGGCTGG AATGGGTGG
30	201	AGTCATTAGT ACTGCTTATA ACTCACACTA CGCGAGCTGG
	241	GCAAAAGGCC GATTCAACCAT CTCCAGAACCC TCGACCACGG
	281	TGGATCTGAA AATGACCAGT CTGACAACCG AAGACACGGC
	321	CACCTATTTC TGTGCCAGAG GGGTAGTTG GTTGGATCTC
	361	TGGGGCCAGG GCACCCCTGGT CACCGTCTCC TCAGGGCAAC
35	401	CTAAGGCTCC ATCAGTCTTC CCACCTGGCCC CCTGCTGCAG
	441	GGACACACCCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
	481	AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAAC

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      521 CGGGCACCCCT CACCAATGGG GTACGCACCT TCCCCGTCCGT
      561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
      601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
      641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
      681 GCCCTCGACA TGCAGCAAGC CCACGTGCC ACCCCCCTGAA
      721 CTCCTGGGGG GACCGTCTGT CTTCATCTTC CCCCCAAAAC
      761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
      801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCAGGGTG
      841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
      881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
      921 CCGCGTGGTC AGCACCCCTCC CCATCGCGCA CCAGGACTGG
      961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
     1001 CACTCCCGC CCCCCATCGAG AAAACCATCT CCAAAGCCAG
     1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
     1081 CCCCAGGGAGG AGCTGAGCAG CAGGTGGTC AGCCTGACCT
     1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA
     1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
     1200 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
     1241 ACAACAAGCT CTCAGTGCCA ACGAGTGAGT GGCAGCGGGG
     1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGCAC
     1321 AACCACTACA CGCAGAAGTC CATCTCCGC TCTCCGGGTA
     1361 AA

```

In another embodiment, the invention provides a M83 020B08L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08L light chain is provided below (SEQ ID NO:58).

```

1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
41 VTIKCQASQS ISTYLDWYQQ KPGQPPKLLI YDASDLASGV
30 81 PSRFKGSGSG TQFTLTISDL ECADAATYYC QQGYTHSNVD
121 NVFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC

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35 A nucleic acid sequence for this M83 020B08L anti-CD83 light chain is provided below (SEQ ID NO:59).

```

1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
5 121 GTCACCATCA AGTGCCAGGC CAGTCAGAGC ATTAGTACCT
161 ACTTAGACTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
201 GCTCCTGATC TATGATGCAT CCGATCTGGC ATCTGGGGTC
241 CCATCGCGGT TCAAAGGCAG TGGATCTGGG ACACAGTTCA
281 CTCTCACCAT CAGCGACCTG GAGTGTGCCG ATGCTGCCAC
10 321 TTACTACTGT CAACAGGGTT ATACACATAG TAATGTTGAT
361 AATGTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
401 ATCCAGTTGC ACCTACTGTG CTCCTCTTCC CACCATCTAG
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
481 GCGAATAAAAT ACTTCCCAGA TGTCACCGTC ACCTGGGAGG
15 521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A
20

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In another embodiment, the invention provides a M83 020B08H heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08H heavy chain is provided below (SEQ ID NO:60).

```

25 1 METGLRWLLL VAVLKGVQCO SVEESGGRLV TPGTPLTLTC
41 TVSGFSLSSY DMTWVRQAPG KGLEWIGIIY ASGTTYYANW
81 AKGRFTISKRT STTVDLKVT S PTIGDTATYF CAREGAGVSM
121 TLWGPGLVLT VSSGQPKAPS VFPLAPCCGD TPSSTVTLGC
161 LVKGYLPEPV TVTWNSGTLT NGVRTFPSVR QSSGLYSLSS
30 201 VVSVTSSSQP VTCNVAHPAT NTKVDKTVAP STCSKPTCPP
241 PELLGGPSVF IFPPPKPKDTL MISRTPEVTC VVVDVSQDDP
281 EVQFTWYINN EQVRTARPPL REQQFNSTIR VVSTLPIAHQ
321 DWLRGKEFKC KVHNKALPAP IEKTISKARG QPLEPKVYTM
361 GPPREELSSR SVSLTCMING FYP PSDISVWE EKNGKAEDNY
35 401 KTTPAVLSDS GSYFLYNKLS VPTSEWQRGD VFTCSVMEHA
441 LHNHYTQKSI SRSPGK

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A nucleic acid sequence for this M83 020B08H anti-CD83 heavy chain is provided below (SEQ ID NO:61).

```

40 1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
41 TCAAAGGTGT CCAGTGTCAAG TCGGTGGAGG AGTCGGGGGG
81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGTCTCTG GATTCTCCCT CAGCAGCTAC GACATGACCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGATCGG
45 201 AATCATTAT GCTAGTGGTA CCACATACTA CGCGAACTGG
241 GCGAAAGGCC GATTCAACCAT CTCCAAAACC TCGACCAACGG
281 TGGATCTGAA AGTCACCAAGT CCGACAATCG GGGACACGGC
321 CACCTATTTC TGTGCCAGAG AGGGGGCTGG TGTTAGTATG
361 ACCTTGCGGG GCCCAGGCAC CCTGGTCACC GTCTCCTCAG
50 401 GGCAACCTAA GGCTCCATCA GTCTCCCAC TGGCCCCCTG

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441 CTGCGGGAC ACACCCTCTA GCACGGTGAC CTTGGGCTGC
481 CTGGTCAAAG GCTACCTCCC GGAGGCCAGTG ACCGTGACCT
521 GGAACTCGGG CACCCCTCACC AATGGGGTAC GCACCTTCCC
561 GTCCGTCCGG CAGTCCTCAG GCCTCTACTC GCTGAGCAGC
5 601 GTGGTGAGCG TGACCTCAAG CAGCCAGCCC GTCACCTGCA
641 ACGTGGCCCA CCCAGCCACC AACACCAAAG TGGACAAGAC
681 CGTTGCGCCC TCGACATGCA GCAAGCCCAC GTGCCCAACCC
721 CCTGAACCTCC TGGGGGGACC GTCTGTCTTC ATCTTCCCCC
761 CAAAACCCAA GGACACCCCTC ATGATCTCAC GCACCCCCGA
10 801 GGTACCATGC GTGGTGGTGG ACGTGAGCCA GGATGACCCC
841 GAGGTGCAGT TCACATGGTA CATAAACAAAC GAGCAGGTGC
881 GCACCGCCCG GCCGCGCTA CGGGAGCAGC AGTTCAACAG
921 CACGATCCGC GTGGTCAGCA CCCTCCCCAT CGCGCACAG
961 GACTGGCTGA GGGGCAAGGA GTTCAAGTGC AAAGTCCACA
15 1001 ACAAGGCACT CCCGGCCCCC ATCGAGAAAA CCATCTCCAA
1041 AGCCAGAGGG CAGCCCCCTGG AGCCGAAGGT CTACACCATG
1081 GGCCTCCCCC GGGAGGAGCT GAGCAGCAGG TCGGTCAAGCC
1121 TGACCTGCAT GATCAACGGC TTCTACCCCTT CCGACATCTC
1161 GGTGGAGTGG GAGAAGAACG GGAAGGCAGA GGACAACATAC
20 1201 AAGACCAACGC CGGCCGTGCT GGACAGCGAC GGCTCCTACT
1241 TCCTCTACAA CAAGCTCTCA GTGCCACGA GTGAGTGGCA
1281 GCGGGGCGAC GTCTTCACCT GCTCCGTGAT GCACGAGGCC
1321 TTGCACAAACC ACTACACGCA GAAGTCCATC TCCCGCTCTC
1361 CGGGTAAA

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25

In another embodiment, the invention provides a M83 006G05L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L light chain is provided below (SEQ ID NO:62).

```

30      1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
        41 VAIKCQASQS VSSYLAWYQQ KPGQPPKPLI YEASMLAAGV
        81 SSRFKGSGSG TDFTLTISDL ECDDAATYYC QQGYSISIDID
        121 NAFFGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
        161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
35      201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC

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A nucleic acid sequence for M83 006G05L anti-CD83 light chain is provided below (SEQ ID NO:63).

```

40      1 ATGGACATGA GGGCCCCAC TCAACTGCTG GGGCTCCTGC
        41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
        81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
        121 GTCGCCATCA AGTGCCAGGC CAGTCAGAGC GTTAGTAGTT
        161 ACTTAGCCTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
        201 GCCCCTGATC TACGAAGCAT CCATGCTGGC GGCTGGGGTC
45      241 TCATCGCGGT TCAAAGGCAG TGGATCTGGG ACAGACTTCA
        281 CTCTCACCAT CAGCGACCTG GAGTGTGACG ATGCTGCCAC

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321 TTACTATTGT CAACAGGGTT ATTCTATCAG TGATATTGAT
361 AATGCTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
401 ATCCAGTTGC ACCTACTGTC CTCCCTTCC CACCATCTAG
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
5 481 GCGAATAAAT ACITTCGGCA TGTCAACCGTC ACCTGGGAGG
521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
10 681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A

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In another embodiment, the invention provides a M83 006G05L heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L heavy chain is provided below (SEQ ID NO:64).

```

15
1 METGLRWLLL VAVLKGVQCQ SVEESGRLV SPGTPLTLTC
41 TASGFSLSSY DMSWVRQAPG KGLEYIGIIS SSGSTYYASW
81 AKGRFTISKI STTVDLEVTS LTTEDTATYF CSREHAGYSG
121 DTGHLWGP GT LTVSSGQPK APSVFPLAPC CGDTPSSTVT
20 161 LGCLVKGYLP EPVTVTWNSG TLTNGVRTFP SVRQSSGLYS
201 LSSVSVTSS SQPVTCNVAH PATNTKVDKT VAPSTCSKPT
241 CPPPELLGGP SVFIFPPKPK DTLMISRTPE VTCVVVDVSQ
281 DDPEVQFTWY INNEQVRTAR PPLREQQFNS TIRVVSTLPI
321 AHQDWLRGKE FKCKVHNKAL PAPIEKTISK ARGQPLEPKV
25 361 YTMGPPREEL SSRSVSLTCM INGFYP PSDIS VEWEKNGKAE
401 DNYKTTPAVL DSDGSYFLYN KLSVPTSEWQ RGDVFTCSV
441 HEALHNHYTQ KSISRSPGK

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A nucleic acid sequence for this M83 006G05L anti-CD83 heavy chain is  
30 provided below (SEQ ID NO:65).

```

1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
41 TCAAAGGTGT CCAGTGTCAAG TCGGTGGAGG AGTCCGGGGG
81 TCGCCTGGTC TCGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGCCTCTG GATTCTCCCT CAGTAGCTAC GACATGAGCT
35 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATAACATCGG
201 AATCATTAGT AGTAGTGGTA GCACATACTA CGCGAGCTGG
241 GCGAAAGGCC GATTCAACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGGA AGTGACCAAGT CTGACAACCG AGGACACGGC
321 CACCTATTTTC TGTAGTAGAG AACATGCTGG TTATAGTGGT
40 361 GATACTGGTC ACTTGTGGGG CCCAGGCACC CTGGTCACCG
401 TCTCCTCGGG GCAACCTAAG GCTCCATCAG TCTTCCCACCT
441 GGCCCCCTGC TGCGGGGACA CACCCCTCTAG CACGGTGACC
481 TTGGGCTGCC TGGTCAAAGG CTACCTCCCG GAGCCAGTGA
521 CCGTGACCTG GAACTCGGGC ACCCTCACCA ATGGGGTACG
45 561 CACCTCCCCG TCCGTCCGGC AGTCCTCAGG CCTCTACTCG
601 CTGAGCAGCG TGGTGAGCGT GACCTCAAGC AGCCAGCCCG
641 TCACCTGCAA CGTGGCCCCAC CCAGCCACCA ACACCAAAGT
681 GGACAAGACC GTTGCGCCCT CGACATGCAG CAAGCCCCACG
721 TGCCCAACCC CTGAACCTCCT GGGGGGACCG TCTGTCTTCA

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761 TCTTCCCCCC AAAACCCAAG GACACCCTCA TGATCTCACG  
801 CACCCCCGAG GTCACATGCG TGGTGGTGGGA CGTGAGGCCAG  
841 GATGACCCCG AGGTGCAGTT CACATGGTAC ATAAACAAACG  
881 AGCAGGTGCG CACCGCCCGG CCGCCGCTAC GGGAGCAGCA  
· 5 921 GTTCAACAGC ACGATCCGCG TGGTCAGCAC CCTCCCCATC  
961 GCGCACCAGG ACTGGCTGAG GGGCAAGGAG TTCAAGTGCA  
1001 AAGTCCACAA CAAGGCACTC CCGGCCCCCA TCGAGAAAAC  
1041 CATCTCCAAA GCCAGAGGGC AGCCCCTGGA GCCGAAGGTC  
1081 TACACCATGG GCCCTCCCCG GGAGGAGCTG AGCAGCAGGT  
10 1121 CGGTCAAGCCT GACCTGCAAT ATCAACGGCT TCTACCCCTTC  
1162 CGACATCTCG GTGGAGTGGG AGAAGAACGG GAAGGCAGAG  
1201 GACAACATACA AGACCACGCC GCCCGTGCTG GACAGCGACG  
1241 GCTCCTACTT CCTCTACAAAC AAGCTCTCAG TGCCCACGAG  
1281 TGAGTGGCAG CGGGGCGACG TCTTCACCTG CTCCGTGATG  
15 1321 CACGAGGCCT TGCACAAACCA CTACACGCAG AAGTCCATCT  
1361 CCCGCTCTCC GGGTAAA

### Anti-sense Nucleic Acids

20 Anti-sense nucleic acids can be used to inhibit the function of CD83. In general, the function of CD83 RNA is inhibited, for example, by administering to a mammal a nucleic acid that can inhibit the functioning of CD83 RNA. Nucleic acids that can inhibit the function of a CD83RNA can be generated from coding and non-coding regions of the CD83 gene. However, nucleic acids that 25 can inhibit the function of a CD83 RNA are often selected to be complementary to CD83 nucleic acids that are naturally expressed in the mammalian cell to be treated with the methods of the invention. In some embodiments, the nucleic acids that can inhibit CD83 RNA functions are complementary to CD83 sequences found near the 5' end of the CD83 coding region. For example, 30 nucleic acids that can inhibit the function of a CD83 RNA can be complementary to the 5' region of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10.

A nucleic acid that can inhibit the functioning of a CD83 RNA need not be 100% complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ 35 ID NO:10. Instead, some variability the sequence of the nucleic acid that can inhibit the functioning of a CD83 RNA is permitted. For example, a nucleic acid that can inhibit the functioning of a CD83 RNA from a human can be complementary to a nucleic acid encoding either a human or a mouse CD83 gene product.

Moreover, nucleic acids that can hybridize under moderately or highly stringent hybridization conditions to a nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 are sufficiently complementary to inhibit the functioning of a CD83 RNA and can be utilized in the methods of  
5 the invention.

"Stringent hybridization conditions" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization are somewhat sequence dependent, and may differ depending upon the environmental conditions of the nucleic acid. For example, longer sequences tend to hybridize specifically at  
10 higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Laboratory Techniques in Biochemistry and Molecular biology-Hybridization with Nucleic Acid Probes, page 1, chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays"  
Elsevier, New York (1993). See also, J. Sambrook et al., Molecular Cloning: A  
15 Laboratory Manual, Cold Spring Harbor Press, N.Y., pp 9.31-9.58 (1989); J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y. (3rd ed. 2001).

Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the  
20 specific double-stranded sequence at a defined ionic strength and pH. For example, under "highly stringent conditions" or "highly stringent hybridization conditions" a nucleic acid will hybridize to its complement to a detectably greater degree than to other sequences (e.g., at least 2- fold over background). By controlling the stringency of the hybridization and/or washing conditions  
25 nucleic acids that are 100% complementary can be hybridized.

For DNA-DNA hybrids, the  $T_m$  can be approximated from the equation of Meinkoth and Wahl Anal. Biochem. 138:267-284 (1984):

$$T_m = 81.5^\circ\text{C} + 16.6 (\log M) + 0.41 (\%GC) - 0.61 (\% \text{ form}) - 500/L$$

where M is the molarity of monovalent cations, %GC is the percentage of  
30 guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The  $T_m$  is the temperature (under defined ionic strength and pH) at which

50% of a complementary target sequence hybridizes to a perfectly matched probe.

Very stringent conditions are selected to be equal to the  $T_m$  for a particular probe.

5 Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity can hybridize. Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for  
10 short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.

Exemplary low stringency conditions include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl and 0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1.0 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 60°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at  
20 37°C, and a wash in 0.1X SSC at 60 to 65°C.

The degree of complementarity or sequence identity of hybrids obtained during hybridization is typically a function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. The type and length of hybridizing nucleic acids also affects whether  
25 hybridization will occur and whether any hybrids formed will be stable under a given set of hybridization and wash conditions.

An example of stringent hybridization conditions for hybridization of complementary nucleic acids that have more than 100 complementary residues on a filter in a Southern or Northern blot is 50% formamide with 1 mg of heparin  
30 at 42°C, with the hybridization being carried out overnight. An example of highly stringent conditions is 0.15 M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (see also, Sambrook, infra). Often, a high stringency wash is preceded by a low

stringency wash to remove background probe signal. An example of medium stringency for a duplex of, e.g., more than 100 nucleotides, is 1x SSC at 45°C for 15 minutes. An example low stringency wash for a duplex of, e.g., more than 100 nucleotides, is 4-6x SSC at 40°C for 15 minutes. For short probes (e.g., 5 about 10 to 50 nucleotides), stringent conditions typically involve salt concentrations of less than about 1.0M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3, and the temperature is typically at least about 30°C.

Stringent conditions can also be achieved with the addition of 10 destabilizing agents such as formamide. In general, a signal to noise ratio of 2x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization. Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the proteins that they encode are substantially identical. 15 This occurs, e.g., when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code.

The following are examples of sets of hybridization/wash conditions that may be used to detect and isolate homologous nucleic acids that are substantially identical to reference nucleic acids of the present invention: a reference 20 nucleotide sequence preferably hybridizes to the reference nucleotide sequence in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO<sub>4</sub>, 1 mM EDTA at 50°C with washing in 2X SSC, 0.1% SDS at 50°C, more desirably in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO<sub>4</sub>, 1 mM EDTA at 50°C with washing in 1X SSC, 0.1% SDS at 50°C, more desirably still in 7% sodium dodecyl sulfate (SDS), 0.5 25 M NaPO<sub>4</sub>, 1 mM EDTA at 50°C with washing in 0.5X SSC, 0.1% SDS at 50°C, preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO<sub>4</sub>, 1 mM EDTA at 50°C with 30 washing in 0.1X SSC, 0.1% SDS at 50°C, more preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO<sub>4</sub>, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 65°C.

In general, T<sub>m</sub> is reduced by about 1°C for each 1% of mismatching. Thus, T<sub>m</sub>, hybridization, and/or wash conditions can be adjusted to hybridize to sequences of the desired sequence identity. For example, if sequences with >90% identity are sought, the T<sub>m</sub> can be decreased 10°C. Generally, stringent

conditions are selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4°C lower than the thermal melting point ( $T_m$ ); moderately stringent conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10°C lower than the thermal melting point ( $T_m$ ); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20°C lower than the thermal melting point ( $T_m$ ).

If the desired degree of mismatching results in a  $T_m$  of less than 45°C (aqueous solution) or 32°C (formamide solution), it is preferred to increase the SSC concentration so that a higher temperature can be used. An extensive guide to the hybridization of nucleic acids is found in Tijssen (1993) *Laboratory Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Acid Probes*, Part 1, Chapter 2 (Elsevier, New York); and Ausubel et al., eds. (1995) *Current Protocols in Molecular Biology*, Chapter 2 (Greene Publishing and Wiley - Interscience, New York). See Sambrook et al. (1989) *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Plainview, New York). Using these references and the teachings herein on the relationship between  $T_m$ , mismatch, and hybridization and wash conditions, those of ordinary skill can generate variants of the present homocysteine S-methyltransferase nucleic acids.

Precise complementarity is therefore not required for successful duplex formation between a nucleic acid that can inhibit a CD83 RNA and the complementary coding sequence of a CD83 RNA. Inhibitory nucleic acid molecules that comprise, for example, 2, 3, 4, or 5 or more stretches of contiguous nucleotides that are precisely complementary to a CD83 coding sequence, each separated by a stretch of contiguous nucleotides that are not complementary to adjacent CD83 coding sequences, can inhibit the function of CD83 RNA. In general, each stretch of contiguous nucleotides is at least 4, 5, 6, 7, or 8 or more nucleotides in length. Non-complementary intervening sequences are preferably 1, 2, 3, or 4 nucleotides in length. One skilled in the art can easily use the calculated melting point of an anti-sense nucleic acid hybridized to a sense nucleic acid to determine the degree of mismatching that

will be tolerated between a particular anti-sense nucleic acid and a particular CD83 RNA.

Nucleic acids that complementary a CD83 RNA can be administered to a mammal or to directly to the site of the inappropriate immune system activity.

- 5 Alternatively, nucleic acids that are complementary to a CD83 RNA can be generated by transcription from an expression cassette that has been administered to a mammal. For example, a complementary RNA can be transcribed from a CD83 nucleic acid that has been inserted into an expression cassette in the 3' to 5' orientation, that is, opposite to the usual orientation employed to generate
- 10 sense RNA transcripts. Hence, to generate a complementary RNA that can inhibit the function of an endogenous CD83 RNA, the promoter would be positioned to transcribe from a 3' site towards the 5' end of the CD83 coding region.

In some embodiments an RNA that can inhibit the function of an

- 15 endogenous CD83 RNA is an anti-sense oligonucleotide. The anti-sense oligonucleotide is complementary to at least a portion of the coding sequence of a gene comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Such anti-sense oligonucleotides are generally at least six nucleotides in length, but can be about 8, 12, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides long.
- 20 Longer oligonucleotides can also be used. CD83 anti-sense oligonucleotides can be provided in a DNA construct and introduced into cells whose division is to be decreased, for example, into CD4+ T cells, Th-1 cells, Th-2 cells or lymphocyte precursor cells.

Anti-sense oligonucleotides can be composed of deoxyribonucleotides, ribonucleotides, or a combination of both. Oligonucleotides can be synthesized endogenously from transgenic expression cassettes or vectors as described herein. Alternatively, such oligonucleotides can be synthesized manually or by an automated synthesizer, by covalently linking the 5' end of one nucleotide with the 3' end of another nucleotide with non-phosphodiester internucleotide linkages such as alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, alkylphosphonates, phosphoramidates, phosphate esters, carbamates, acetamide, carboxymethyl esters, carbonates, and phosphate

triesters. See Brown, 1994, Meth. Mol. Biol. 20:1-8; Sonveaux, 1994, Meth. Mol. Biol. 26:1-72; Uhlmann et al., 1990, Chem. Rev. 90:543-583.

CD83 anti-sense oligonucleotides can be modified without affecting their ability to hybridize to a CD83 RNA. These modifications can be internal or at 5 one or both ends of the anti-sense molecule. For example, internucleoside phosphate linkages can be modified by adding peptidyl, cholesteryl or diamine moieties with varying numbers of carbon residues between these moieties and the terminal ribose. Modified bases and/or sugars, such as arabinose instead of ribose, or a 3', 5'-substituted oligonucleotide in which the 3' hydroxyl group or 10 the 5' phosphate group are substituted, can also be employed in a modified anti-sense oligonucleotide. These modified oligonucleotides can be prepared by methods available in the art. Agrawal et al., 1992, Trends Biotechnol. 10:152-158; Uhlmann et al., 1990, Chem. Rev. 90:543-584; Uhlmann et al., 1987, Tetrahedron. Lett. 215:3539-3542.

15 In one embodiment of the invention, expression of a CD83 gene is decreased using a ribozyme. A ribozyme is an RNA molecule with catalytic activity. See, e.g., Cech, 1987, Science 236: 1532-1539; Cech, 1990, Ann. Rev. Biochem. 59:543-568; Cech, 1992, Curr. Opin. Struct. Biol. 2: 605-609; Couture and Stinchcomb, 1996, Trends Genet. 12: 510-515. Ribozymes can be used to 20 inhibit gene function by cleaving an RNA sequence, as is known in the art (see, e.g., Haseloff et al., U.S. Pat. No. 5,641,673).

CD83 nucleic acids complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 can be used to generate ribozymes that will specifically bind to mRNA transcribed from a CD83 gene. Methods of 25 designing and constructing ribozymes that can cleave other RNA molecules in trans in a highly sequence specific manner have been developed and described in the art (see Haseloff et al. (1988), Nature 334:585-591). For example, the cleavage activity of ribozymes can be targeted to specific RNAs by engineering a discrete "hybridization" region into the ribozyme. The hybridization region 30 contains a sequence complementary to the target RNA and thus specifically hybridizes with the target (see, for example, Gerlach et al., EP 321,201). The target sequence can be a segment of about 10, 12, 15, 20, or 50 contiguous nucleotides selected from a nucleotide sequence shown in SEQ ID NO:1, SEQ

ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Longer complementary sequences can be used to increase the affinity of the hybridization sequence for the target. The hybridizing and cleavage regions of the ribozyme can be integrally related; thus, upon hybridizing to the target RNA through the complementary regions, the 5 catalytic region of the ribozyme can cleave the target.

#### **Other CD83 Modulating Molecules**

A wide variety of molecules may be used to modulate CD83 activity or function. Such molecules can also be used to modulate the immune system 10 independent of CD83. Compositions and methods for modulating CD83 activity or expression can include these molecules as well as other components. Representative examples that are discussed in more detail below include transcription factors, RNA-binding factors, organic molecules, or peptides.

15    ***RNA-Binding Factors:***

One class of molecules that can be used to modulate cytokine levels or GM-CSF levels by way of the CD83 gene is the RNA binding factors. Such factors include those described in PCT/EP01/14820 and other sources.

For example, the HuR protein (Genbank accession number U38175) has 20 the ability to specifically bind to CD83 RNA at AU-rich elements or sites. Such AU-rich elements comprise sequences such as AUUUA (SEQ ID NO:49), AUUUUA (SEQ ID NO:50) and AUUUUUA (SEQ ID NO:51). Binding by such HuR proteins to CD83 mRNA is thought to increase the stability, transport and translation of CD83 mRNA, and thereby increase the expression of CD83 25 polypeptides. Hence, CD83 expression may be increased by administering HuR proteins or nucleic acids to a mammal.

Conversely, CD83 expression may be decreased by administering factors that block HuR binding to CD83 mRNA. Factors that block HuR binding include proteins or nucleic acids that can bind to the AU-rich elements normally 30 bound by HuR, for example, nucleic acids or anti-sense nucleic acids that are complementary to AU-rich elements.

*Organic Molecules:*

Numerous organic molecules may be used to modulate the immune system. These compounds include any compound that can interact with a component of the immune system. Such compounds may interact directly with CD83, indirectly with 5 CD83 or with some other polypeptide, cell or factor that plays a role in the function of the immune system. In some embodiments, the organic molecule can bind to a CD83 polypeptide or a CD83 nucleic acid.

Organic molecules can be tested or assayed for their ability to modulate CD83 activity, CD83 function or for their ability to modulate components of the 10 immune system. For example, within one embodiment of the invention suitable organic molecules may be selected either from a chemical library, wherein chemicals are assayed individually, or from combinatorial chemical libraries where multiple compounds are assayed at once, then deconvoluted to determine and isolate the most active compounds.

15 Representative examples of such combinatorial chemical libraries include those described by Agrafiotis et al., "System and method of automatically generating chemical compounds with desired properties," U.S. Patent No. 5,463,564; Armstrong, R.W., "Synthesis of combinatorial arrays of organic compounds through the use of multiple component combinatorial array syntheses," 20 WO 95/02566; Baldwin, J.J. et al., "Sulfonamide derivatives and their use," WO 95/24186; Baldwin, J.J. et al., "Combinatorial dihydrobenzopyran library," WO 95/30642; Brenner, S., "New kit for preparing combinatorial libraries," WO 95/16918; Chenera, B. et al., "Preparation of library of resin-bound aromatic carbocyclic compounds," WO 95/16712; Ellman, J.A., "Solid phase and 25 combinatorial synthesis of benzodiazepine compounds on a solid support," U.S. Patent No. 5,288,514; Felder, E. et al., "Novel combinatorial compound libraries," WO 95/16209; Lerner, R. et al., "Encoded combinatorial chemical libraries," WO 93/20242; Pavia, M.R. et al., "A method for preparing and selecting pharmaceutically useful non-peptide compounds from a structurally diverse 30 universal library," WO 95/04277; Summerton, J.E. and D.D. Weller, "Morpholino-subunit combinatorial library and method," U.S. Patent No. 5,506,337; Holmes, C., "Methods for the Solid Phase Synthesis of Thiazolidinones, Metathiazanones, and Derivatives thereof," WO 96/00148; Phillips, G.B. and G.P. Wei, "Solid-phase

Synthesis of Benzimidazoles," *Tet. Letters* 37:4887-90, 1996; Ruhland, B. et al., "Solid-supported Combinatorial Synthesis of Structurally Diverse  $\square\Delta$ -Lactams," *J. Amer. Chem. Soc.* 111:253-4, 1996; Look, G.C. et al., "The Identification of Cyclooxygenase-1 Inhibitors from 4-Thiazolidinone Combinatorial Libraries," 5 *Bioorg and Med. Chem. Letters* 6:707-12, 1996.

*Peptides:*

Peptide molecules that modulate the immune system may be obtained through the screening of combinatorial peptide libraries. Such libraries may either 10 be prepared by one of skill in the art (see e.g., U.S. Patent Nos. 4,528,266 and 4,359,535, and Patent Cooperation Treaty Publication Nos. WO 92/15679, WO 92/15677, WO 90/07862, WO 90/02809, or purchased from commercially available sources (e.g., New England Biolabs Ph.D.<sup>TM</sup> Phage Display Peptide Library Kit).

15

**Methods of Using the CD83 Mutant Mouse**

In one embodiment, the invention provides a method for identifying ligands, receptors, therapeutic drugs and other molecules that can modulate the phenotype of the mutant CD83 in vivo. This method involves administering a 20 test compound to the mutant CD83 mouse of the invention and observing whether the compound causes a change in the phenotype of the mutant mouse. Changes in phenotype that are of interest include increases or decreases in T cells (especially CD4+ T cells), increases or decreases in GMCSF, IL-2, IL-4 or IL-10 cytokine production, increases or decreases in inflammation, increases or 25 decreases in dendritic cell function and other T cell responses known to one of skill in the art.

Test compounds can be screened in vitro to ascertain whether they interact directly with CD83. In vitro screening can, for example, identify whether a test compound or molecule can bind to the cytoplasmic tail or the 30 membrane-associated portions of CD83. Such information, combined with observation of the in vivo phenotype before and after administration of the test compound provides further insight into the function of CD83 and provides

targets for manipulation T cell activation and other functions modulated by CD83.

The invention is not limited to identification of molecules that directly associate with CD83. The in vivo screening methods provided herein can, also 5 identify test compounds that have an indirect effect on CD83, or that partially or completely replace a function of CD83.

Increases or decreases in T cell numbers can be observed in blood samples or in samples obtained from thymus, spleen or lymph node tissues. In order to observe the activation of T cells and/or the interaction of T cells and 10 dendritic cells, dendritic cells can be pulsed with antigens ex vivo and then injected into mice to prime CD4+ T cells in draining lymphoid organs. See Inaba et al., J. Exp. Med. 172: 631-640, 1990; Liu, et al., J. Exp. Med. 177: 1299-1307, 1993; Sornasse et al., J. Exp. Med. 175: 15-21, 1992. Antigens can also be deposited intramuscularly and dendritic cells from the corresponding 15 afferent lymphatics can carry that antigen in a form stimulatory for T cells. Bujdoso et al., J. Exp. Med. 170: 1285-1302, 1989. According to the invention, factors stimulating the interaction of dendritic cells with T cells in vivo can be identified by administering antigens in this manner and then observing how T cell respond, e.g. by observing whether T cell activation occurs.

20 Increases or decreases in cytokine levels can be observed by methods provided herein or by other methods available in the art.

### Compositions

The CD83 polypeptides and antibodies of the invention, including their 25 salts, are administered so as to achieve a reduction in at least one symptom associated with an infection, indication or disease.

To achieve the desired effect(s), the polypeptide or antibody, a variant thereof or a combination thereof, may be administered as single or divided dosages, for example, of at least about 0.01 mg/kg to about 500 to 750 mg/kg, of 30 at least about 0.01 mg/kg to about 300 to 500 mg/kg, at least about 0.1 mg/kg to about 100 to 300 mg/kg or at least about 1 mg/kg to about 50 to 100 mg/kg of body weight, although other dosages may provide beneficial results. The amount administered will vary depending on various factors including, but not limited to,

the polypeptide or antibody chosen, the disease, the weight, the physical condition, the health, the age of the mammal, whether prevention or treatment is to be achieved, and if the polypeptide or antibody is chemically modified. Such factors can be readily determined by the clinician employing animal models or  
5 other test systems that are available in the art.

Administration of the therapeutic agents in accordance with the present invention may be in a single dose, in multiple doses, in a continuous or intermittent manner, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or  
10 prophylactic, and other factors known to skilled practitioners. The administration of the CD83 polypeptides and antibodies of the invention may be essentially continuous over a preselected period of time or may be in a series of spaced doses. Both local and systemic administration is contemplated.

To prepare the composition, CD83 polypeptides and antibodies are  
15 synthesized or otherwise obtained, purified as necessary or desired and then lyophilized and stabilized. The polypeptide or antibody can then be adjusted to the appropriate concentration, and optionally combined with other agents. The absolute weight of a given polypeptide or antibody included in a unit dose can vary widely. For example, about 0.01 to about 2 g, or about 0.1 to about 500 mg,  
20 of at least one polypeptide or antibody of the invention, or a plurality of CD83 polypeptides and antibodies specific for a particular cell type can be administered. Alternatively, the unit dosage can vary from about 0.01 g to about 50 g, from about 0.01 g to about 35 g, from about 0.1 g to about 25 g, from about 0.5 g to about 12 g, from about 0.5 g to about 8 g, from about 0.5 g to about 4 g,  
25 or from about 0.5 g to about 2 g.

Daily doses of the CD83 polypeptides or antibodies of the invention can vary as well. Such daily doses can range, for example, from about 0.1 g/day to about 50 g/day, from about 0.1 g/day to about 25 g/day, from about 0.1 g/day to about 12 g/day, from about 0.5 g/day to about 8 g/day, from about 0.5 g/day to about 4 g/day, and from about 0.5 g/day to about 2 g/day.  
30

Thus, one or more suitable unit dosage forms comprising the therapeutic CD83 polypeptides or antibodies of the invention can be administered by a variety of routes including oral, parenteral (including subcutaneous, intravenous,

intramuscular and intraperitoneal), rectal, dermal, transdermal, intrathoracic, intrapulmonary and intranasal (respiratory) routes. The therapeutic CD83 polypeptides or antibodies may also be formulated for sustained release (for example, using microencapsulation, see WO 94/ 07529, and U.S. Patent 5 No.4,962,091). The formulations may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known to the pharmaceutical arts. Such methods may include the step of mixing the therapeutic agent with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if 10 necessary, introducing or shaping the product into the desired delivery system.

When the therapeutic CD83 polypeptides or antibodies of the invention are prepared for oral administration, they are generally combined with a pharmaceutically acceptable carrier, diluent or excipient to form a pharmaceutical formulation, or unit dosage form. For oral administration, the 15 CD83 polypeptides or antibodies may be present as a powder, a granular formulation, a solution, a suspension, an emulsion or in a natural or synthetic polymer or resin for ingestion of the active ingredients from a chewing gum. The active CD83 polypeptides or antibodies may also be presented as a bolus, electuary or paste. Orally administered therapeutic CD83 polypeptides or 20 antibodies of the invention can also be formulated for sustained release, e.g., the CD83 polypeptides or antibodies can be coated, micro-encapsulated, or otherwise placed within a sustained delivery device. The total active ingredients in such formulations comprise from 0.1 to 99.9% by weight of the formulation.

By "pharmaceutically acceptable" it is meant a carrier, diluent, excipient, 25 and/or salt that is compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations containing the therapeutic CD83 polypeptides or antibodies of the invention can be prepared by procedures known in the art using well-known and readily available ingredients. For example, the 30 polypeptide or antibody can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, solutions, suspensions, powders, aerosols and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include buffers, as well as fillers and extenders

such as starch, cellulose, sugars, mannitol, and silicic derivatives. Binding agents can also be included such as carboxymethyl cellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone. Moisturizing agents  
5 can be included such as glycerol, disintegrating agents such as calcium carbonate and sodium bicarbonate. Agents for retarding dissolution can also be included such as paraffin. Resorption accelerators such as quaternary ammonium compounds can also be included. Surface active agents such as cetyl alcohol and glycerol monostearate can be included. Adsorptive carriers such as kaolin and  
10 bentonite can be added. Lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols can also be included. Preservatives may also be added. The compositions of the invention can also contain thickening agents such as cellulose and/or cellulose derivatives. They may also contain gums such as xanthan, guar or carbo gum or gum arabic, or alternatively  
15 polyethylene glycols, bentones and montmorillonites, and the like.

For example, tablets or caplets containing the CD83 polypeptides or antibodies of the invention can include buffering agents such as calcium carbonate, magnesium oxide and magnesium carbonate. Caplets and tablets can also include inactive ingredients such as cellulose, pregelatinized starch, silicon dioxide, hydroxy propyl methyl cellulose, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide, benzoic acid, citric acid, corn starch, mineral oil, polypropylene glycol, sodium phosphate, zinc stearate, and the like.  
20 Hard or soft gelatin capsules containing at least one polypeptide or antibody of the invention can contain inactive ingredients such as gelatin, microcrystalline cellulose, sodium lauryl sulfate, starch, talc, and titanium dioxide, and the like, as well as liquid vehicles such as polyethylene glycols (PEGs) and vegetable oil.  
25 Moreover, enteric-coated caplets or tablets containing one or more CD83 polypeptides or antibodies of the invention are designed to resist disintegration in the stomach and dissolve in the more neutral to alkaline environment of the duodenum.  
30

The therapeutic CD83 polypeptides or antibodies of the invention can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular,

subcutaneous, intraperitoneal or intravenous routes. The pharmaceutical formulations of the therapeutic CD83 polypeptides or antibodies of the invention can also take the form of an aqueous or anhydrous solution or dispersion, or alternatively the form of an emulsion or suspension or salve.

5        Thus, the therapeutic CD83 polypeptides or antibodies may be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small volume infusion containers or in multi-dose containers. As noted above, preservatives can be added to help maintain the  
10      shelf life of the dosage form. The active CD83 polypeptides or antibodies and other ingredients may form suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active CD83 polypeptides or antibodies and other ingredients may be in powder form, obtained by aseptic  
15      isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

These formulations can contain pharmaceutically acceptable carriers, vehicles and adjuvants that are well known in the art. It is possible, for example, to prepare solutions using one or more organic solvent(s) that is/are acceptable  
20      from the physiological standpoint, chosen, in addition to water, from solvents such as acetone, ethanol, isopropyl alcohol, glycol ethers such as the products sold under the name "Dowanol," polyglycols and polyethylene glycols, C<sub>1</sub>-C<sub>4</sub> alkyl esters of short-chain acids, ethyl or isopropyl lactate, fatty acid triglycerides such as the products marketed under the name "Miglyol," isopropyl myristate,  
25      animal, mineral and vegetable oils and polysiloxanes.

It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes, flavorings and colorings. Antioxidants such as t-butylhydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and  $\alpha$ -tocopherol and its  
30      derivatives can be added.

Also contemplated are combination products that include one or more CD83 polypeptides or antibodies of the present invention and one or more other anti-microbial agents. For example, a variety of antibiotics can be included in the

pharmaceutical compositions of the invention, such as aminoglycosides (e.g., streptomycin, gentamicin, sisomicin, tobramycin and amicacin), ansamycins (e.g. rifamycin), antimycotics (e.g. polyenes and benzofuran derivatives),  $\beta$ -lactams (e.g. penicillins and cephalosporins), chloramphenical (including thiamphenol and azidamphenicol), linosamides (lincomycin, clindamycin), macrolides (erythromycin, oleandomycin, spiramycin), polymyxins, bacitracins, tyrothycin, capreomycin, vancomycin, tetracyclines (including oxytetracycline, minocycline, doxycycline), phosphomycin and fusidic acid.

Additionally, the CD83 polypeptides or antibodies are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active polypeptide or antibody, for example, in a particular part of the intestinal or respiratory tract, possibly over a period of time. Coatings, envelopes, and protective matrices may be made, for example, from polymeric substances, such as polylactide-glycolates, liposomes, microemulsions, microparticles, nanoparticles, or waxes. These coatings, envelopes, and protective matrices are useful to coat indwelling devices, e.g., stents, catheters, peritoneal dialysis tubing, draining devices and the like.

For topical administration, the therapeutic agents may be formulated as is known in the art for direct application to a target area. Forms chiefly conditioned for topical application take the form, for example, of creams, milks, gels, dispersion or microemulsions, lotions thickened to a greater or lesser extent, impregnated pads, ointments or sticks, aerosol formulations (e.g., sprays or foams), soaps, detergents, lotions or cakes of soap. Other conventional forms for this purpose include wound dressings, coated bandages or other polymer coverings, ointments, creams, lotions, pastes, jellies, sprays, and aerosols. Thus, the therapeutic CD83 polypeptides or antibodies of the invention can be delivered via patches or bandages for dermal administration. Alternatively, the polypeptide or antibody can be formulated to be part of an adhesive polymer, such as polyacrylate or acrylate/vinyl acetate copolymer. For long-term applications it might be desirable to use microporous and/or breathable backing laminates, so hydration or maceration of the skin can be minimized. The backing layer can be any appropriate thickness that will provide the desired

protective and support functions. A suitable thickness will generally be from about 10 to about 200 microns.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents.

- 5      Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active CD83 polypeptides or antibodies can also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122; 4,383,529; or 4,051,842. The percent  
10     by weight of a therapeutic agent of the invention present in a topical formulation will depend on various factors, but generally will be from 0.01% to 95% of the total weight of the formulation, and typically 0.1-85% by weight.

- 15     Drops, such as eye drops or nose drops, may be formulated with one or more of the therapeutic CD83 polypeptides or antibodies in an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs. Drops can be delivered via a simple eye dropper-capped bottle, or via a plastic bottle adapted to deliver liquid contents dropwise, via a specially shaped closure.

- 20     The therapeutic polypeptide or antibody may further be formulated for topical administration in the mouth or throat. For example, the active ingredients may be formulated as a lozenge further comprising a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the composition in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes  
25     comprising the composition of the present invention in a suitable liquid carrier.

The pharmaceutical formulations of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and salts of the type that are available in the art.

Examples of such substances include normal saline solutions such as

- 30     physiologically buffered saline solutions and water. Specific non-limiting examples of the carriers and/or diluents that are useful in the pharmaceutical formulations of the present invention include water and physiologically

acceptable buffered saline solutions such as phosphate buffered saline solutions pH 7.0-8.0.

The CD83 polypeptides or antibodies of the invention can also be administered to the respiratory tract. Thus, the present invention also provides aerosol pharmaceutical formulations and dosage forms for use in the methods of the invention. In general, such dosage forms comprise an amount of at least one of the agents of the invention effective to treat or prevent the clinical symptoms of a specific infection, indication or disease. Any statistically significant attenuation of one or more symptoms of an infection, indication or disease that has been treated pursuant to the method of the present invention is considered to be a treatment of such infection, indication or disease within the scope of the invention.

Alternatively, for administration by inhalation or insufflation, the composition may take the form of a dry powder, for example, a powder mix of the therapeutic agent and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges, or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator, insufflator, or a metered-dose inhaler (see, for example, the pressurized metered dose inhaler (MDI) and the dry powder inhaler disclosed in Newinan, S. P. in Aerosols and the Lung, Clarke, S. W. and Davia, D. eds., pp. 197-224, Butterworths, London, England, 1984).

Therapeutic CD83 polypeptides or antibodies of the present invention can also be administered in an aqueous solution when administered in an aerosol or inhaled form. Thus, other aerosol pharmaceutical formulations may comprise, for example, a physiologically acceptable buffered saline solution containing between about 0.1 mg/ml and about 100 mg/ml of one or more of the CD83 polypeptides or antibodies of the present invention specific for the indication or disease to be treated. Dry aerosol in the form of finely divided solid polypeptide or antibody or nucleic acid particles that are not dissolved or suspended in a liquid are also useful in the practice of the present invention. CD83 polypeptides or antibodies of the present invention may be formulated as dusting powders and comprise finely divided particles having an average particle size of between about 1 and 5  $\mu\text{m}$ , alternatively between 2 and 3  $\mu\text{m}$ . Finely divided particles

may be prepared by pulverization and screen filtration using techniques well known in the art. The particles may be administered by inhaling a predetermined quantity of the finely divided material, which can be in the form of a powder. It will be appreciated that the unit content of active ingredient or ingredients 5 contained in an individual aerosol dose of each dosage form need not in itself constitute an effective amount for treating the particular infection, indication or disease since the necessary effective amount can be reached by administration of a plurality of dosage units. Moreover, the effective amount may be achieved using less than the dose in the dosage form, either individually, or in a series of 10 administrations.

For administration to the upper (nasal) or lower respiratory tract by inhalation, the therapeutic CD83 polypeptides or antibodies of the invention are conveniently delivered from a nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may 15 comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Nebulizers include, but are not limited to, those described in U.S. Patent Nos. 4,624,251; 20 3,703,173; 3,561,444; and 4,635,627. Aerosol delivery systems of the type disclosed herein are available from numerous commercial sources including Fisons Corporation (Bedford, Mass.), Schering Corp. (Kenilworth, NJ) and American Pharmoseal Co., (Valencia, CA). For intra-nasal administration, the therapeutic agent may also be administered via nose drops, a liquid spray, such 25 as via a plastic bottle atomizer or metered-dose inhaler. Typical of atomizers are the Mistometer (Wintrop) and the Medihaler (Riker).

Furthermore, the active ingredients may also be used in combination with other therapeutic agents, for example, pain relievers, anti-inflammatory agents, antihistamines, bronchodilators and the like, whether for the conditions 30 described or some other condition.

The present invention further pertains to a packaged pharmaceutical composition for controlling microbial infections such as a kit or other container. The kit or container holds a therapeutically effective amount of a pharmaceutical

composition for controlling microbial infections and instructions for using the pharmaceutical composition for control of the microbial infection. The pharmaceutical composition includes at least one polypeptide or antibody of the present invention, in a therapeutically effective amount such that the selected disease or immunological condition is controlled.

The invention will be further described by reference to the following detailed examples, which are given for illustration of the invention, and are not intended to be limiting thereof.

10

#### **EXAMPLE 1: Mouse Mutation and Characterization**

##### **Mutant Generation**

Male C57BL6 mice received 3 weekly injections of N-ethyl-N-nitrosourea (ENU) at a concentration of 100mg/kg. N-Ethyl-N-nitrosourea was quantified prior to injection by spectrophotometry. Mice that regained fertility after a minimum period of 12 weeks were then used to generate pedigree founder G1 animals. G1 male mice were crossed to C57BL6J females and their female progeny (G2 animals) crossed back to their fathers to generate G3 animals for screening.

G3 mice were weaned at 3 weeks of age. Each animal then underwent a series of screens designed to assess a number of parameters, including immune function, inflammatory response and bone development. In the initial screen, conducted at 6 weeks of age, 150-200ul of whole blood was collected by retro-orbital bleed into heparinized tubes. Cells were pelleted and red blood cells lysed. Samples were then stained with antibodies to cell surface markers expressed on distinct lymphoid and myeloid sub-populations. These samples were analyzed by flow-cytometry.

##### **Mutant Identification**

A group of 27 G3 mice from 2 different pedigrees, pedigree 9 and pedigree 57 (i.e. derived from 2 distinct G1 fathers) were analyzed in this screen. Two animals from pedigree 9 were identified as having a reduced (>2 standard deviation from normal) percentage of CD4+ T cells in peripheral blood (Figure 1). Both animals were descended from the same G1 and shared the same

mother. All other animals screened on that day had a normal percentage of CD4+ T cells. The number of phenodeviants identified (2 from a litter of 9 animals) was suggestive of a trait controlled by a single gene and inherited in a Mendelian fashion.

5 A second litter generated from Pedigree 9 bred to G2 daughter #4 exhibited an identical phenotype with reduced numbers of CD4+ T cells, further suggesting that the trait had a genetic basis. The phenotype was designated LCD4.1 (Low CD4 Mutant # 1) and was used for mapping experiments.

10 **Mutation Mapping**

In order to map the LCD4.1 mutant phenotype, affected G3 male mice (presumptive homozygous for the mutation) were bred to female animals from the C3HeB/FeJ strain to generate F1 progeny. These F1 females (presumptively heterozygous for the mutation) were then mated back to their affected father to generate N2 progeny.

Blood was collected from N2 animals and flow cytometric analysis was performed to identify CD4+ T cells. For a phenotype controlled by a single gene, breeding homozygous fathers to heterozygous daughters should yield 50% normal N2 animals and 50% affected N2 animals. This ratio of normal to 20 affected animals was observed in the N2 generation: Multiple N2 animals exhibited a reduced percentage of CD4+ T cells, indicating that the phenotype was heritable (Figure 2).

DNA samples were prepared from samples of tail tissue collected from these N2 mice and used for a genome scan, using a collection of assembled 25 markers, and performed on the ABI 3100 DNA analyzer. Initial genetic linkage was seen to the tip of chromosome 13, where the closest microsatellite marker was D13Mit139 with a LOD score of 8.2. By calculating upper and lower confidence limits, the mutant gene was located between 13.4 and 29.6 cM on chromosome 13. Through additional genotyping, this region was reduced to an 30 11 cM interval on chromosome 13. No significant linkage to other chromosomal regions was seen.

### Mutation Identification

A candidate gene, CD83, was identified for gene-testing based upon its reported position within the interval. CD83 has previously been used as a marker of dendritic cell activation, suggesting that it might play a role in dendritic cell function and hence in regulating T cell development and function.

Sequence analysis of the mutant DNA revealed a mutation in the stop codon of CD83. All affected animals were homozygous for this mutation while non-affected animals carried one wild-type allele and one mutant allele (Figure 3 and Figure 4). The mutation destroyed the stop codon and resulted in the addition of a unique 55 amino acid tail to the C-terminus of CD83 (Figure 5).

### Additional Functional Data

A reduction in CD4+ T cells was seen in peripheral blood, spleen tissues and lymph nodes from homozygous LCD4.1 mice. Although there was a reduced number of CD4+ T cells in the thymus there is no overt block in the developmental process and there was no alteration in B cell development in the bone marrow. Histological evaluation of thymus, spleen and lymph nodes from affected mice revealed no gross alteration in tissue architecture.

Dendritic cells can be differentiated from bone marrow of wild type mice by culture in GM-CSF. These cells can be characterized by the surface expression of dendritic cell markers, including CD86 and CD11c. Both LCD4.1 affected and normal animals were capable of giving rise to CD86+CD11c+ cells under these culture conditions. LCD4.1 mutant mice thus were capable of generating dendritic cells under in vitro culture conditions. These data suggest that the phenotype seen in LCD4.1 mice is not due to a failure of dendritic cells to develop but rather may reflect a defect in function.

To track dendritic cells the sensitizing agent FITC was applied to the dorsal surface of the ears of LCD4.1 affected and wild-type mice. FITC was picked up by dendritic cells that then migrated to the draining auricular lymph nodes, where the presence of the FITC label on the dendritic cell surface permitted detection by flow-cytometry. FITC labeled cells expressing CD86 were detected in equal proportions in draining lymph node from normal and affected LCD4.1 mice. These data indicate that LCD4.1 mutant animals are

capable of generating dendritic cells *in vivo* and that these cells are able to pick up antigen in the ear and travel to the draining lymph node.

5                   **EXAMPLE 2: CD83 and CD4+ T Cell Function**

**Materials and Methods**

Spleens were removed from wild type and mutant mice and digested with collagenase to liberate dendritic cells. Spleens were stained for surface expression of CD4 (helper T cells) and CD11c (dendritic cells). Cells expressing 10 these markers were purified by fluorescence activated cell sorting (FACS sorting). CD11c and CD4+ positive cells were also purified from an allogeneic mouse strain, BALBc.

Mixed lymphocyte cultures were set up using purified cell populations. Dendritic cells from BALBc animals were used to stimulate CD4+ T cells from 15 wild type and mutant mice. In a reciprocal experiment dendritic cells prepared from wild type and mutant mice were used to stimulate BALBc CD4+ T cells. After 5 days in culture proliferative responses were measured by incorporation of tritiated thymidine.

Dendritic cells from wild type and mutant mice were both capable of 20 activating allogeneic T cells, suggesting that dendritic cell function was unimpaired in the mutant animal (Figure 6a). In contrast CD4+ T cells from mutant animals exhibited a diminished response after 5 days of stimulation (Figure 6b).

These data suggest that the mutation in the CD83 gene has minimal effect 25 on dendritic cells intrinsic function but rather has a profound effect upon T cell activity. The CD4+ T cell therefore may have a novel requirement for CD83 functionality on T cells during allogeneic activation. CD83 may be influencing the extent of CD4+ T cell activation or altering the duration of the CD4+ T cell proliferative response. The therapeutic manipulation of CD83 may thus 30 represent a mechanism for the specific regulation of T cell function in the treatment of T cell mediated diseases, including autoimmune disorders.

Antibodies capable of blocking CD83 function may be used as therapeutics in

the treatment of immune diseases whilst the activation of CD83 may have utility in enhancing immune responses in cancer and other circumstances.

### Conclusion

5        Although CD83 has been described as a marker of dendritic cell activation there is little data as to its function in vivo. The mutation provided by the invention destabilizes or inactivates the protein and leads to impaired surface expression. As a consequence, CD4+ T cell function is impaired although the development of dendritic cells is not inhibited and mutant dendritic cells retain  
10      functionality. This results in the impaired development of CD4+ T cells. This impaired ability to activate T cells is also seen in a slight decrease in contact sensitivity responses in LCD4.1 mutant mice.

15      **EXAMPLE 3: Mutant CD83 Have Different Cytokine Levels than Wild Type Mice**

This Example demonstrates that CD4<sup>+</sup> T-cells from CD83 mutant animals express higher levels of IL-4 and lower levels of IL-2 compared to CD4<sup>+</sup> T-cells from CD83 wild type animals.

20      **Methods for cell activation and cytokine measurements:**

Spleens cells from 6-8-week-old homozygous CD83 wild type or CD83 mutant (LCD4.1) mice were used to isolate CD4<sup>+</sup> T-cells by positive selection using magnetic beads (Miltenyi Biotec). A 96 round bottom plate was coated  
25      with 50µL per well of a solution containing either 1 or 10 µg/mL of anti-CD3 and 0.1 or 0.2 µg/mL of anti-CD28 antibodies (both from Pharmingen) in PBS overnight. This plate was then washed using 150 µL of PBS three times. To this pre-coated plate, 20,000 CD4<sup>+</sup> T-cells (either wild type or CD83 mutant) were added in a 200 µL final volume of RPMI containing 10% FBS, 55 µM β-  
30      mercaptoethanol and antibiotics. The plates were then incubated in a CO<sub>2</sub> incubator at 37 °C for 44 to 72 hours. For determination of cytokine levels, supernatants were harvested and cytokines were measured using either a Cytometric Bead Array system (Pharmingen) or ELISA (R&D). For RNA

measurements, the cells were harvested and RNA was isolated using Tri reagent (Sigma). IL-10 and IL-4 mRNA levels were measured by reverse transcription and TaqMan (Applied Biosystems) analysis.

5   **Results:**

Figure 7 shows the IL-2, IL-4, IL-5, TNF $\alpha$  and IFN $\gamma$  levels produced by either wild type or CD83 mutant CD4 $^{+}$  T-cells. Purified cells were incubated as described above in the presence of 1 $\mu$ g/mL of anti-CD3 and 0.2  $\mu$ g/mL of anti-CD28 antibodies for 72 hours. The supernatants were then simultaneously 10 analyzed for production of IL-2, IL-4, IL-5, TNF $\alpha$  and IFN $\gamma$  using the cytometric bead array system from Pharmingen.

Figure 7 demonstrates that CD4 $^{+}$  T-cells from CD83 mutant animals expressed higher levels of IL-4 and lower levels of IL-2 compared to CD4 $^{+}$  T-cells from CD83 wild type animals. Other cytokines and a new set of 15 stimulation assays were analyzed including the production levels of IL-10 and GMCSF by these cells (Figures 8 and 9). In both cases, cells from mutant animals produce larger amounts of IL-10 and GMCSF than did wild type animals. Figure 10 shows that mRNA levels for both IL-4 and IL-10 were increased in cells from activated mutant CD83, CD4 $^{+}$  T-cells compared with 20 cells from wild type animals.

**EXAMPLE 4: Anti-CD83 Antibodies May Mimic  
the Effects of the CD83 Mutation**

25   **Methods for antibody testing:**

For modulation of cytokine production by anti-CD83 antibodies, CD4 $^{+}$  T-cells were isolated and activated as mentioned above in the presence of increasing concentrations of anti-CD83 antibodies. For proliferation assays, CD4 $^{+}$  T-cells were isolated from an OT2tg [transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide]. Dendritic 30 cells were isolated from a C57BL6 mouse by a negative selection using B220 magnetic beads (Miltenyi Biotec) followed by positive selection using CD11-c magnetic beads (Miltenyi Biotec). Five thousand CD4 $^{+}$  T-cells were then mixed

with five thousand dendritic cells in a 96 well plate in the presences of 1  $\mu$ M OVA peptide using RPMI (55  $\mu$ M BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO<sub>2</sub> incubator at 37°C and pulsed using [<sup>3</sup>H] thymidine for 8 hours. Cells were then  
5 harvested and [<sup>3</sup>H] thymidine incorporation was quantified using a top counter.

**Results:**

In some assays, anti-CD83 antibodies decreased production of IL-4 by activated CD4<sup>+</sup> T-cells in a dose dependent manner. Different antibody  
10 preparations did provide somewhat different degrees of inhibition of IL-4 production (Figure 11). Accordingly, the epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not IL-4 production is significantly inhibited.

The effects of anti CD83 antibodies on proliferation of a peptide specific  
15 T-cell proliferation assay using the OT2 T-cell receptor (TCR) transgenic system were also observed. CD4<sup>+</sup> T-cells derived from these TCR transgenic animals express high levels of a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide and thus have high levels of proliferation when mixed with antigen presenting cells (dendritic cells were used) in the presence of the OVA  
20 peptide. In such assays, anti-CD83 antibodies were able to decrease proliferation of CD4<sup>+</sup> T-cells in this system (Figure 12). However, different antibody preparations had somewhat different effects on the proliferation of CD4<sup>+</sup> T-cells. Accordingly, the CD83 epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not CD4<sup>+</sup> T-cell proliferation is  
25 significantly inhibited.

**EXAMPLE 5: Increased T-Cell Proliferation  
by Transgenic Expression of CD83**

30 This Example illustrates that over expression of CD83 in transgenic mice leads to increased T-cell proliferation.

**Materials and Methods**

A 34.3 kb fragment of normal mouse genomic DNA, including the ~18 kb coding region of the CD83 gene, as well as ~10.6 kb of upstream flanking sequences and ~5.7 kb of downstream sequences was microinjected into normal mouse one-cell embryos. Four individual founder animals were generated. 5 Transgenic mice were then crossed to a male OT2tg mouse. Male offspring carrying both the CD83 and OT2 transgene were used to analyze peptide specific T-cell proliferation.

For proliferation assays, CD4<sup>+</sup> T-cells and dendritic cells were isolated 10 from either OT2tg [transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide] CD83 wild type or from OT2tg CD83 transgenic mice as described above (Example 4). Five thousand OT2tg CD4<sup>+</sup> T-cells from either wild type or CD83 transgenic animals were then mixed with five thousand wild type dendritic cells or five thousand CD83 transgenic 15 dendritic cells in a 96 well plate in the presence of increasing concentrations of OVA peptide using RPMI (55 μM BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO<sub>2</sub> incubator at 37C and pulsed using [<sup>3</sup>H] thymidine for 8 hours. Cells were then harvested and [<sup>3</sup>H] thymidine incorporation was quantified using a top counter.

20

**Results:**

OT2tg CD4<sup>+</sup> T-cells derived from CD83 transgenic mice proliferated at higher rates than the same cell population derived from a CD83 wild type animal 25 (Figure 13). This increased proliferation was seen at all the concentrations of OVA peptide tested. Whereas OT2tg CD4<sup>+</sup> T-cells derived from CD83 transgenic animals exhibited increased proliferation, dendritic cells from CD83 transgenic animals did not exhibit a substantial increase in proliferation. Therefore, it appears that transgenic expression in the CD4<sup>+</sup> T-cell, and not in dendritic cells is what led to the increased proliferation of CD4<sup>+</sup> T-cells.

30

**EXAMPLE 6: Inhibition of proliferation of PHA activated human PBMCs  
by protein A purified rabbit anti mouse CD83 polyclonal sera.**

This Example shows that antibodies raised against the mouse CD83 protein can inhibit proliferation of human peripheral blood mononuclear cells.

5

**Materials and Methods**

Rabbit polyclonal sera was raised against mouse CD83 protein by immunizing rabbits using a mouse CD83 external domain protein fused to a rabbit Ig domain (Figure 14). Pre-immune sera and anti-mouse polyclonal sera 10 were then purified using a protein A column (Pharmacia Biotech) as described by the manufacturer, then dialyzed against PBS and stored at 4° C. To monitor the recognition of mouse CD83 protein by the polyclonal sera, which was obtained at different dates post immunization, a titer was obtained using an antigen specific ELISA (Figure 15). As illustrated by Figure 15, a good 15 polyclonal response was obtained against the mouse CD83 protein.

Human peripheral blood mononuclear cells (PBMCs) were isolated using a Ficoll gradient (Ficoll Paque Plus, Pharmacia) and washed with PBS buffer. For activation and proliferation studies, five thousand cells were incubated in 200  $\mu$ L of media (RPMI, 10%FBS, antibiotics) and 5ug/mL of *Phaseolus vulgaris* leucoagglutinin (PHA) in the presence or absence of increasing concentrations of Protein A purified pre-immune sera or with similarly purified anti-CD83 polyclonal antibodies. After 48 hours at 37°C in a CO<sub>2</sub> incubator the cells were pulsed with [<sup>3</sup>H] thymidine for ~8 hours and harvested. Thymidine incorporation into the PBMCs was measured using a top counter for analysis.

25

**Results**

Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein. Proliferation of PHA-activated human PBMCs was not affected by 30 addition of increasing concentrations of protein A purified rabbit pre-immune sera. When increasing concentrations of protein A purified rabbit polyclonal sera raised against the mouse CD83 protein was added, a concentration dependent decrease in proliferation was observed.

These data indicate that antibodies raised against the mouse protein are able to cross-react with the human protein. Moreover, antibodies raised against the mouse protein are able to inhibit proliferation of PHA-activated human PBMCs.

5        All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that  
10      certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

**WHAT IS CLAIMED**

1. A method of modulating cytokine production in a mammal by modulating the activity or expression of a CD83 polypeptide.
- 5 2. A method of modulating cytokine production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of a CD83 polypeptide.
- 10 3. A method of modulating cytokine production by a T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.
4. A method of modulating cytokine production by a T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.
- 15 5. A method of modulating a CD4+ T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.
6. A method of modulating a CD4+ T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.
- 20 7. A method of modulating granulocyte macrophage colony stimulating factor production in a mammal by modulating the activity or expression of CD83 polypeptides.
- 25 8. A method of modulating granulocyte macrophage colony stimulating factor production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.
- 30 9. A method of modulating granulocyte macrophage colony stimulating factor production by a T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.

10. A method of modulating granulocyte macrophage colony stimulating factor production by a T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.
- 5 11. A method of tumor necrosis factor production in a mammal by modulating the activity or expression of CD83 polypeptides.
12. A method of modulating tumor necrosis factor production in a mammal by administering to the mammal an antibody that can modulate the activity or 10 expression of CD83 polypeptides.
13. A method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides.
- 15 14. A method of inhibiting proliferation of a human peripheral blood mononuclear cell in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.
15. An antibody that can bind to a CD83 polypeptide comprising SEQ ID 20 NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein activated CD4<sup>+</sup> T-cells produce lower levels of interleukin-4 when said T-cells are contacted with the antibody.
16. An antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein CD4<sup>+</sup> T-cells proliferation is 25 decreased when said T-cells are contacted with the antibody.
17. An antibody comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, 30 SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID

NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

5 18. A nucleic acid encoding an antibody comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ 10 ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

15

19. The nucleic acid of claim 18, wherein the nucleic acid comprises nucleotide sequence SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63 or SEQ ID NO:65.

20

20. A method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ 25 ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ 30 ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

21. A method for decreasing the activity of a CD83 gene product in a mammal, comprising administering to the mammal an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

22. A method for decreasing the translation of a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

23. A method for decreasing the translation of a CD83 gene product in a mammal, comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

24. A method for decreasing proliferation of CD4<sup>+</sup> T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

25. The method of claim 24, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ

ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45,  
SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID  
NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ  
ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

5

26. A method for decreasing interleukin-2 levels and increasing interleukin-4  
levels in a mammal comprising administering to the mammal an antibody that  
can bind to a CD83 gene product, wherein the CD83 gene product comprises  
SEQ ID NO:2 or SEQ ID NO:9.

10

27. The method of claim 26, wherein the antibody SEQ ID NO:11, SEQ ID  
NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ  
ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27,  
SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID  
15 NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ  
ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41,  
SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID  
NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ  
ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58,  
20 SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

28. A method for decreasing interleukin-2 levels and increasing interleukin-4  
levels in a mammal comprising administering to the mammal a nucleic acid  
complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID  
25 NO:3, SEQ ID NO:5, or SEQ ID NO:10.

29. The method of claim 26 or 28, wherein the interleukin-2 levels are  
decreased and the interleukin-4 levels are increased to treat an autoimmune  
disease.

30

30. The method of claim 29, wherein the autoimmune disease is diabetes  
mellitus, arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis,  
osteoarthritis, psoriatic arthritis, multiple sclerosis, myasthenia gravis, systemic

lupus erythematosus, autoimmune thyroiditis, dermatitis, atopic dermatitis,  
eczematous dermatitis, psoriasis, Sjogren's Syndrome, keratoconjunctivitis sicca  
secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to  
arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis,  
5 keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus  
erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal  
reactions, erythema nodosum leprosum, autoimmune uveitis, allergic  
encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic  
bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell  
10 anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis,  
chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen  
planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary  
cirrhosis, uveitis posterior, or interstitial lung fibrosis.

15 31. The method of claim 26 or 28, wherein the interleukin-2 levels are  
decreased and the interleukin-4 levels are increased to stimulate production of  
Th2-associated cytokines in transplant recipients.

20 32. The method of claim 31, wherein the Th2-associated cytokines prolong  
survival of transplanted tissue.

33. The method of claim 32, wherein the transplanted tissue is skin, cardiac  
or bone marrow.

25 34. The method of claim 26 or 28, wherein the mammal is a human.

35. A method for increasing interleukin-10 levels in a mammal comprising  
administering to the mammal an antibody that can bind to a CD83 gene product,  
wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.  
30

36. The method of claim 35, wherein the antibody comprises SEQ ID NO:11,  
SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID  
NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ

ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31,  
SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID  
NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ  
ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45,  
5 SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID  
NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ  
ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

37. A method for increasing interleukin-10 levels in a mammal comprising  
10 administering to the mammal a nucleic acid complementary to a CD83 nucleic  
acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID  
NO:10.

38. The method of claim 35 or 37, wherein the interleukin-10 levels are  
15 increased to treat neoplastic disease.

39. The method of claim 35 or 37, wherein the interleukin-10 levels are  
increased to treat a tumor.

20 40. A method for increasing interleukin-2 levels in a mammal comprising  
administering to the mammal a functional CD83 polypeptide that comprises SEQ  
ID NO:9.

41. A method for increasing interleukin-2 levels in a mammal comprising:  
25 (a) transforming a T cell from the mammal with a nucleic acid  
encoding a functional CD83 polypeptide operably linked to a  
promoter functional in a mammalian cell, to generate a  
transformed T cell;  
(b) administering the transformed T cell to the mammal to provide  
30 increased levels of interleukin-2.

42. The method of claim 41, wherein the CD83 polypeptide comprises SEQ  
ID NO:9.

43. The method of claim 41, wherein the nucleic acid comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

5 44. The method of claim 41, wherein the mammal is a human.

45. The method of claim 41, wherein the interleukin-2 levels are increased to treat an allergy or an infectious disease.

10 46. The method of claim 45, wherein the infectious disease is related to HIV infection, tuberculosis, leishmaniasis, schistosomiasis, filarial nematode infection, or intestinal nematode infection.

15 47. The method of claim 45, wherein the infectious disease is related to infection by *Aeromonas* spp., *Bacillus* spp., *Bacteroides* spp., *Campylobacter* spp., *Clostridium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Gastospirillum* sp., *Helicobacter* spp., *Klebsiella* spp., *Salmonella* spp., *Shigella* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Vibrio* spp., or *Yersinia* spp.

20 48. The method of claim 45, wherein the infectious disease is related to staph infection, typhus, food poisoning, bacillary dysentery, pneumonia, cholera, an ulcer, diarrhea, hemorrhagic colitis, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.

25 49. The method of claim 45, wherein the infectious disease is related to infection by *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Escherichia coli O157:H7*, *Shigella dysenteria*, *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Vivrio cholerae*, *Helicobacter pylori*, a multiply-resistant strain of *Staphylococcus aureus*, a vancomycin-resistant strain of *Enterococcus faecium*, or a vancomycin-resistant strain of *Enterococcus faecalis*.

30 50. The method of claim 45, wherein the infectious disease is related to infection by a virus.

51. The method of claim 50, wherein the virus is a hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, poxvirus, herpes virus, adenovirus, papovavirus, parvovirus, reovirus, orbivirus, picornavirus,  
5 rotavirus, alphavirus, rubivirus, influenza virus type A, influenza virus type B, flavivirus, coronavirus, paramyxovirus, morbillivirus, pneumovirus, rhabdovirus, lyssavirus, orthomyxovirus, bunyavirus, phlebovirus, nairovirus, hepadnavirus, arenavirus, retrovirus, enterovirus, rhinovirus or filovirus.

10 52. A method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

15 53. The method of claim 52, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

25

54. A method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

30

55. A method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide.

56. A method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide.

5 57. The method of claim 55 or 56, wherein the mammal is human and the CD83 polypeptide comprises SEQ ID NO:9.

10 58. A method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mutant mouse and observing whether CD4+ T cells become activated, wherein the somatic and germ cells of the mutant mouse comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8.

15 59. A mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8.

60. The mutant CD83 gene of claim 63 comprising nucleotide sequence SEQ ID NO:3.

20 61. A mutant mouse whose somatic and germ cells comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of said mutant CD83 gene reduces CD4+T cell activation.

25 62. The mutant mouse of claim 61, wherein the mutant CD83 gene comprises SEQ ID NO:3.

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	Mom	G3 ID	% CD4+
Pedigree 57	G2 # 1	57.1.1	22
		57.1.2	26
		57.1.3	24
	G2 # 4	57.4.1	15
		57.4.2	18
	G2 # 5	57.5.1	21
		57.5.2	19
		57.5.3	24
		57.5.4	22
		57.5.5	19
		57.5.6	17
Pedigree 9	G2 # 4	9.4.1	6
		9.4.2	20
		9.4.3	16
		9.4.4	12
		9.4.5	20
		9.4.6	15
		9.4.7	24
		9.4.8	27
		9.4.9	5
	G2 # 5	9.5.1	18
		9.5.2	20
		9.5.3	22
		9.5.4	20
		9.5.5	22
		9.5.6	20
		9.5.7	23

average	19.1
stdev	5.2
= + 2SD	29.6
= -2SD	8.7

FIG. 1

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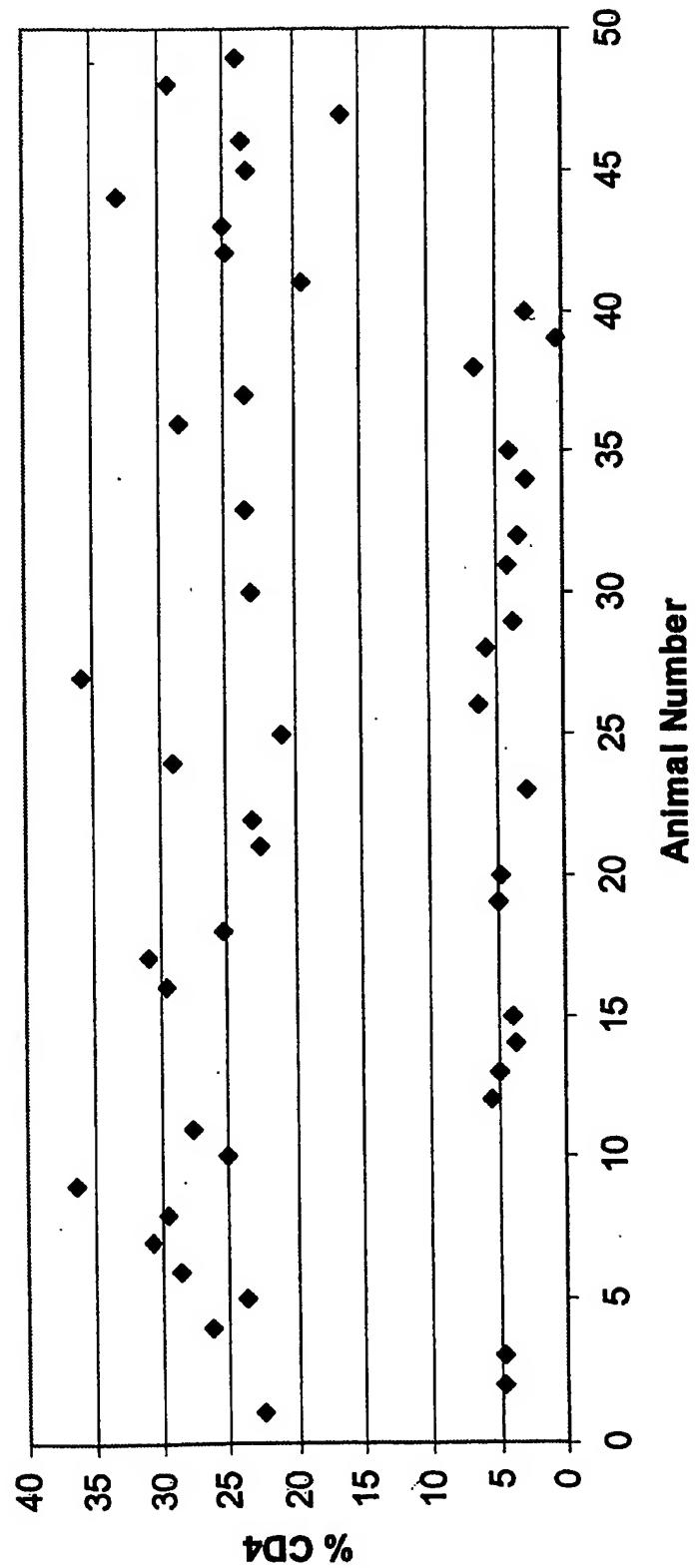


FIG. 2

3/20

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 51 CCTGCAGCCT GGCACCCGCG ATGGCGATGC GGGAGGTGAC GGTGGCTTGC  
 101 TCCGAGACCG CCGACTTGCC TTGCACAGCG CCCTGGGACC CGCAGCTCTC  
 151 CTATGCAGTG TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG  
 201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC CAGGAGAAGG  
 251 GCCTATTCCC TGACGATCCA AAACACTACC ATCTGCAGCT CGGGCACCTA  
 301 CAGGTGTGCC CTGCAGGAGC TCGGAGGGCA GCGCAACTTG AGCGGCACCG  
 351 TGGTTCTGAA GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC  
 401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG TTGTTTTCTA  
 451 CCTGACACTC ATCATTTCA CCTGCAAATT TGCACGACTA CAAAGCATTT  
 501 TCCCAGATAT TTCTAAACCT GGTACGGAAC AAGCTTTCT TCCAGTCACC  
 551 TCCCCAAGCA AACATTGGG GCCAGTGACC CTTCCTAAGA CAGAACGGT  
 601 ATGAGTAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA CATCAGATCA  
 651 GTGTGCCTGA ATGCCACCCG GACAAGAGAA GAATGAGCTC CATCCTCAGA  
 701 TGGCAACCTT TCTTTGAAGT CCTTCACCTG ACAGTGGGCT CCACACTACT  
 751 CCCTGACACA GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA  
 801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG GCTATCTGGT  
 851 CAACCTCGTG AGTGCCTTTC AGTCATCTAC AAGCTATGGT GAGATGCAGG  
 901 TGAAGCAGGG TCATGGGAAA TTTGAACACT CTGAGCTGGC CCTGTGACAG  
 951 ACTCCTGAGG ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTGAA  
 1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC TGGCGGAAAT  
 1051 TGACAGGCCA AGCTGTGAGC CAGTGGGAAA TATTTAGCAA ATAATTTCCC  
 1101 AGTGCAGAGG TCCTGCTATT AGTAAGGGAT ATTATGTGTA CATAGAAATG  
 1151 AGAGGTCAGT GAACTATTCC CCAGCAGGGC CTTTCATCT GGAAAAGACA  
 1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT TTTAATCTT  
 1251 CATGTACTTG TCAAAGAAGA ATTTTCATG TTTTTCAAA GAAGTGTGTT  
 1301 TCTTCCTTT TTTAAAATAT GAAGGTCTAG TTACATAGCA TTGCTAGCTG  
 1351 ACAAGCAGCC TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA  
 1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA CAATGGACTG  
 1451 AGAAACCAGA AGTCTGGCCA CAAGATTGTC TGTATGATTC TGGACGAGTC  
 1501 ACTTGTGGTT TTCACTCTCT GGTTAGTAAA CCAGATAGTT TAGTCTGGGT  
 1551 TGAATACAAT GGATGTGAAG TTGCTGGGG AAAGCTGAAT GTAGTGAATA  
 1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT AGAGTTCTGG  
 1651 AGCTGAGCGA ATGCCGTCA TATCTCAGCT TGCCCATCAA TCCAAACACA  
 1701 GGAGGCTACA AAAAGGACAT GAGCATGGTC TTCTGTGTGA ACTCCTCCTG  
 1751 AGAAAACGTGG AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA  
 1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGGCCACG ACAGGAGGAA  
 1851 GTTCTCAGAT GTTGCATTGA TGTAACATTG TTGCATTCT TTAATGAGCT  
 1901 GGGCTCCTTC CTCATTTGCT TCCCAAAGAG ATTTTGTCCC ACTAATGGTG  
 1951 TGCCCATCAC CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC  
 2001 GTGCTTACCT CTCAGCCATG ACTTCATGC TATTAAAAGA ATGCATGTGA  
 2051 A

FIG. 3

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1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT CTAGGCTGCG  
 51 CCTGCAGCCT GGCACCCGCG ATGGCGATGC GGGAGGTGAC GGTGGCTTGC  
 101 TCCGAGACCG CCGACTTGCC TTGCACAGCG CCCTGGGACC CGCAGCTCTC  
 151 CTATGCAGTG TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG  
 201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC CAGGAGAAGG  
 251 GCCTATTCCC TGACGATCCA AAACACTACC ATCTGCAGCT CGGGCACCTA  
 301 CAGGTGTGCC CTGCAGGAGC TCGGAGGGCA GCGCAACTTG AGCGGCACCG  
 351 TGGTTCTGAA GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC  
 401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG TTGTTTTCTA  
 451 CCTGACACTC ATCATTTCAT CCTGCAAATT TGCACGACTA CAAAGCATT  
 501 TCCCAGATAT TTCTAACCT GGTACGGAAC AAGCTTTCT TCCAGTCACC  
 551 TCCCCAAGCA AACATTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT  
 601 AAGAGTAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA CATCAGATCA  
 651 GTGTGCCTGA ATGCCACCCG GACAAGAGAA GAATGAGCTC CATCCTCAGA  
 701 TGGCAACCTT TCTTGAAAGT CCTTCACCTG ACAGTGGGCT CCACACTACT  
 751 CCCTGACACA GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA  
 801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG GCTATCTGGT  
 851 CAACCTCGTG AGTGCTTTTC AGTCATCTAC AAGCTATGGT GAGATGCAGG  
 901 TGAAGCAGGG TCATGGAAA TTTGAACACT CTGAGCTGGC CCTGTGACAG  
 951 ACTCCTGAGG ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTGAA  
 1001 TTTGTCCGTG TTCGTTGCAC CAGCCCAGAT GTCTCACATC TGGCGGAAAT  
 1051 TGACAGGCCA AGCTGTGAGC CAGTGGAAA TATTTAGCAA ATAATTTCCC  
 1101 AGTGCGAAGG TCCTGCTATT AGTAAGGAGT ATTATGTGTA CATAGAAATG  
 1151 AGAGGTCAGT GAACTATTCC CCAGCAGGGC CTTTCATCT GGAAAAGACA  
 1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT TTTAATCTT  
 1251 CATGTACTTG TCAAAGAAGA ATTTTCATG TTTTTCAAA GAAGTGTGTT

FIG. 4A

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1301 TCTTCCTTT TTTAAAATAT GAAGGTCTAG TTACATAGCA TTGCTAGCTG  
1351 ACAAGCAGCC TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA  
1401 AGCTAGAACGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA CAATGGACTG  
1451 AGAAACCAGA AGTCTGGCCA CAAGATTGTC TGTATGATTC TGGACGAGTC  
1501 ACTTGTGGTT TTCACTCTCT GGTTAGTAAA CCAGATAGTT TAGTCTGGGT  
1551 TGAATACAAT GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA  
1601 CATTGGCAAC TCTACTGGC TGTTACCTTG TTGATATCCT AGAGTTCTGG  
1651 AGCTGAGCGA ATGCCTGTCA TATCTCAGCT TGCCCATCAA TCCAAACACA  
1701 GGAGGCTACA AAAAGGACAT GAGCATGGTC TTCTGTGTGA ACTCCTCCTG  
1751 AGAAACGTGG AGACTGGCTC AGCGCTTGC GCTTGAAGGA CTAATCACAA  
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG ACAGGAGGAA  
1851 GTTCTCAGAT GTTGCATTGA TGTAACATTG TTGCATTCT TTAATGAGCT  
1901 GGGCTCCTTC CTCATTGCT TCCCAAAGAG ATTTTGTCCC ACTAATGGTG  
1951 TGCCCATCAC CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC  
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA ATGCATGTGA  
2051 A

**FIG. 4B**

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**Wild Type Amino Acid Sequence for CD83 protein [Mus musculus]**  
MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP WDPQLSYAVS  
WAKVSESGTE SVELPESKQN SSFEAPRRRA YSLTIQNTTI CSSGTYRCAL  
QELGGQRNLS GTVVLKVTGC PKEATESTFR KYRAEAVLLF SLVVFYLTLLI  
IFTCKFARLQ SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV

**Mutant CD83 Amino Acid Sequence: novel tail underlined, in bold.**  
MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP WDPQLSYAVS  
WAKVSESGTE SVELPESKQN SSFEAPRRRA YSLTIQNTTI CSSGTYRCAL  
QELGGQRNLS GTVVLKVTGC PKEATESTFR KYRAEAVLLF SLVVFYLTLLI  
IFTCKFARLQ SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV**RVGS**  
**PLVFTKPRAH QISVPECHPD KRRMSSIILRW QPFFEVLHLT VGSTLLPDTG**  
**S**

FIG. 5

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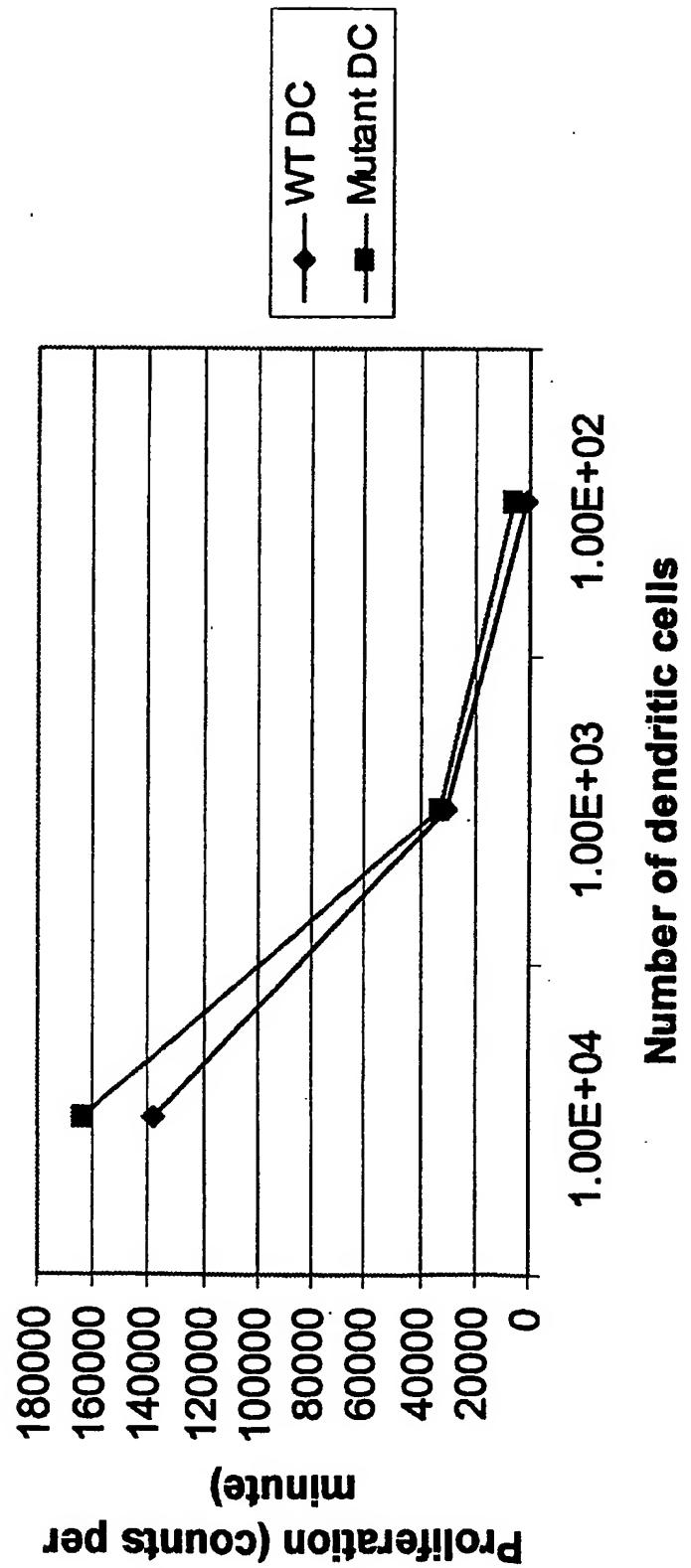


FIG. 6A

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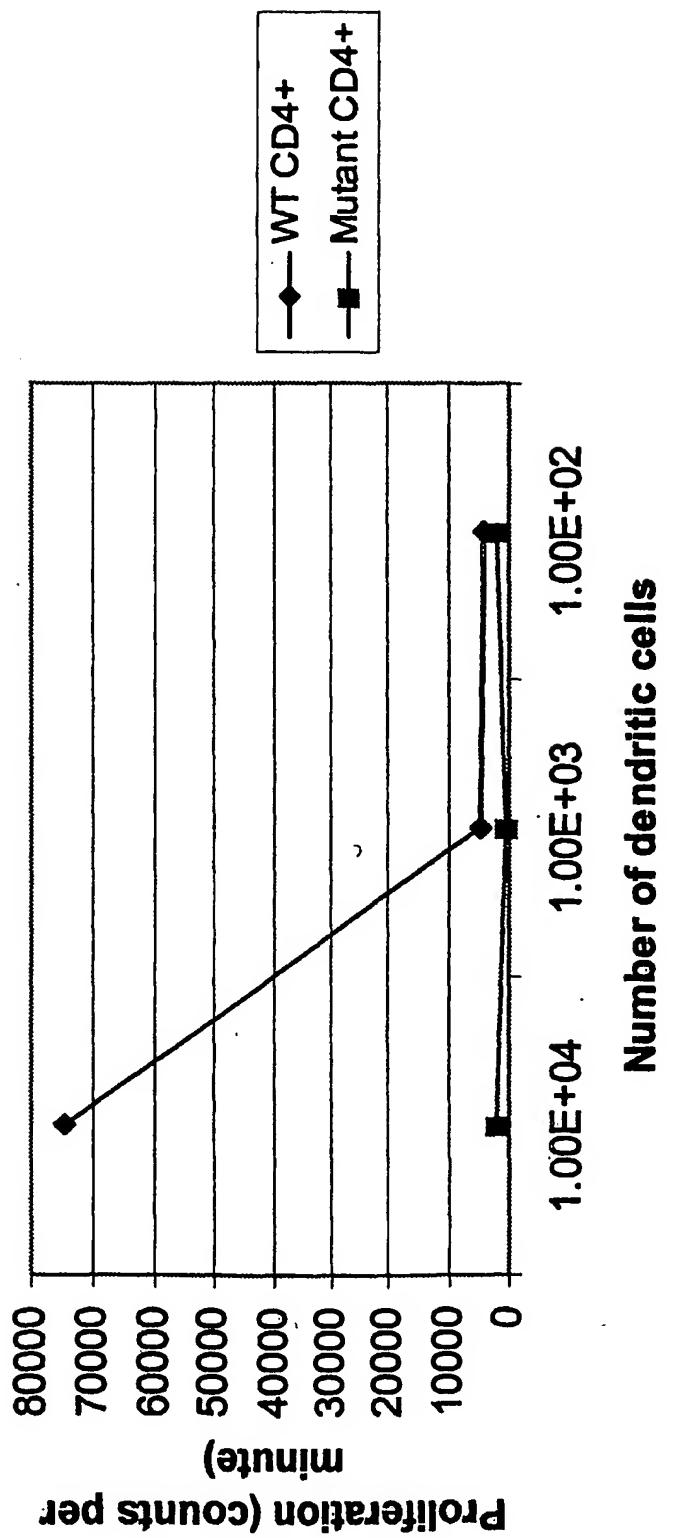


FIG. 6B

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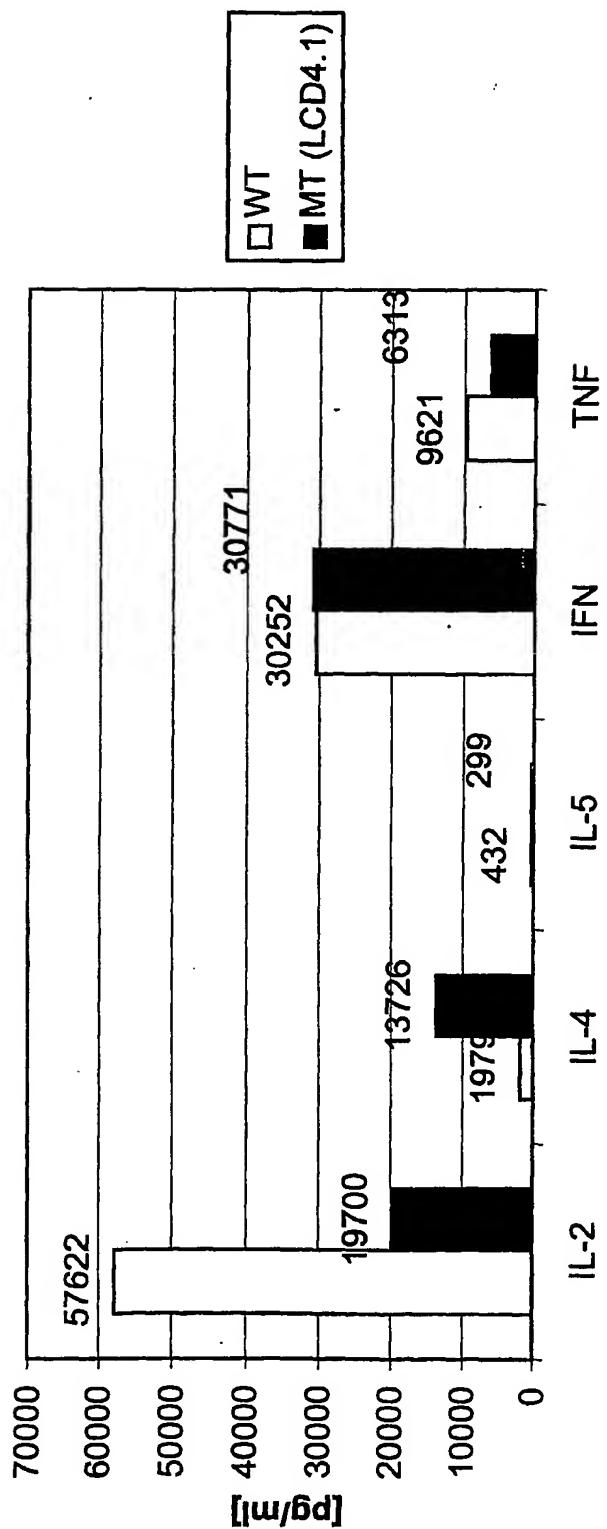


FIG. 7

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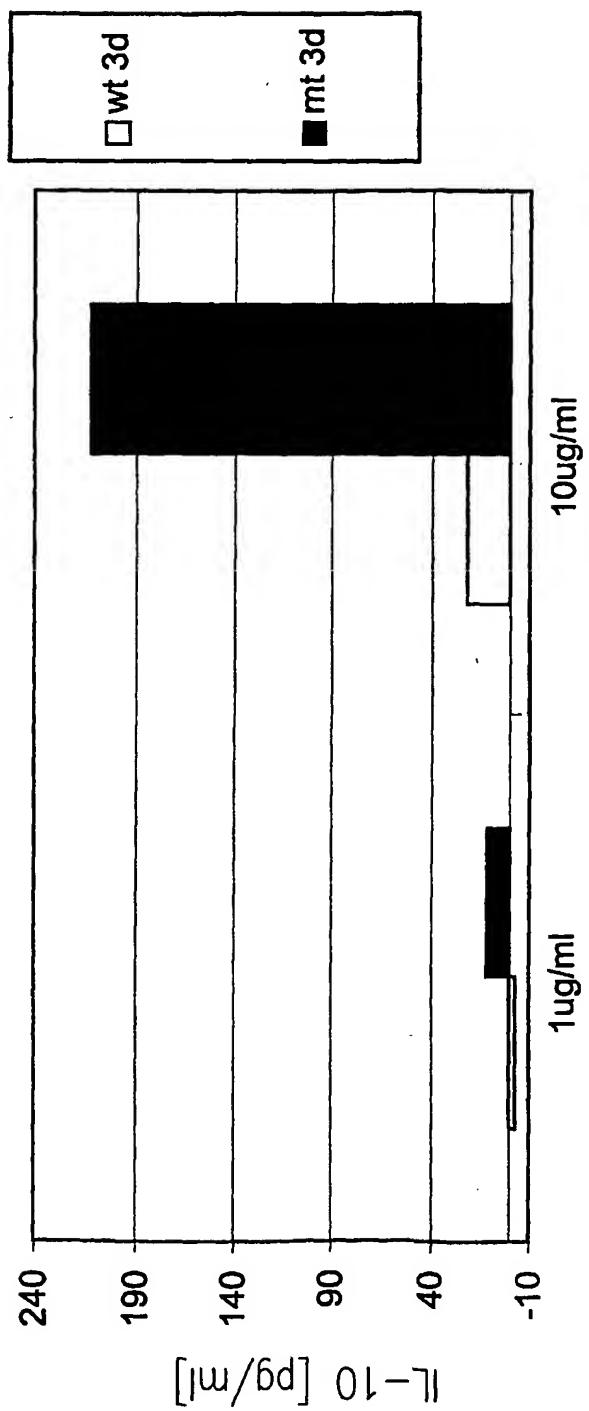


FIG. 8

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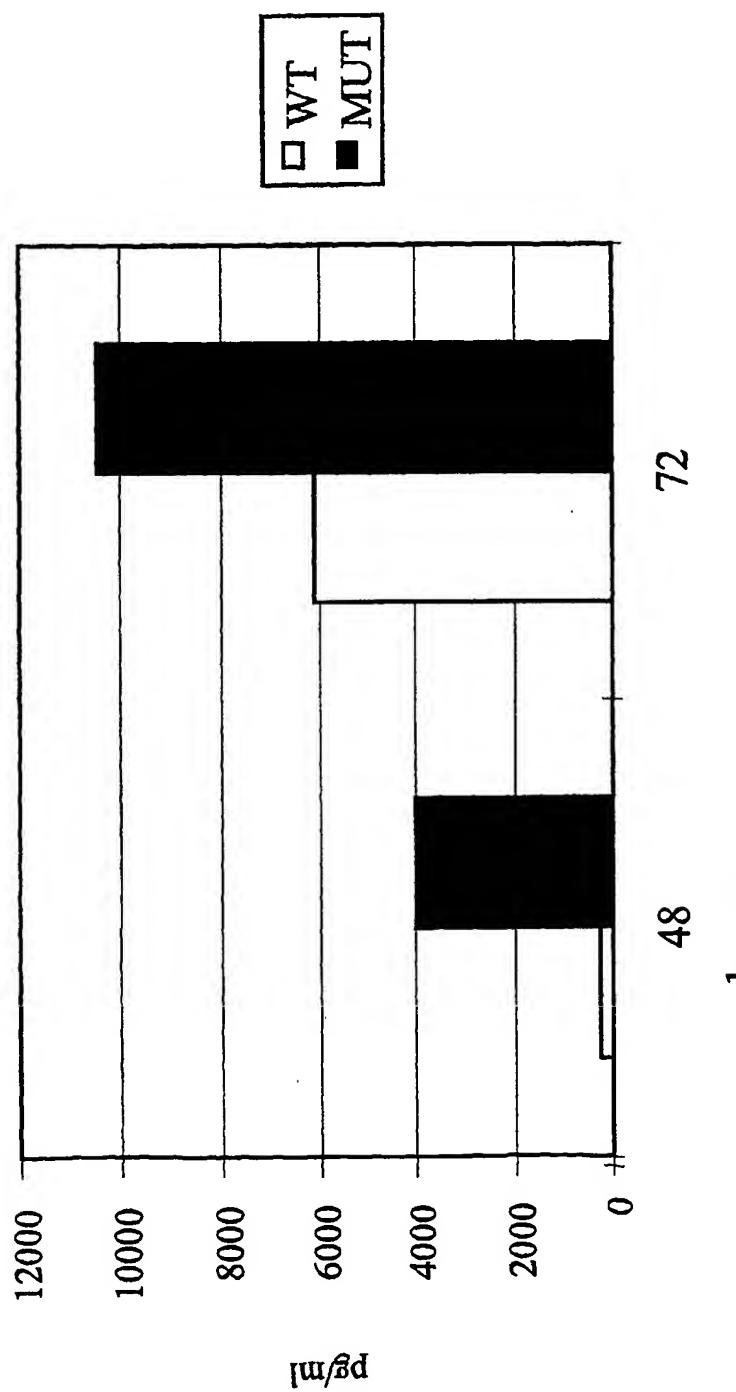


FIG. 9

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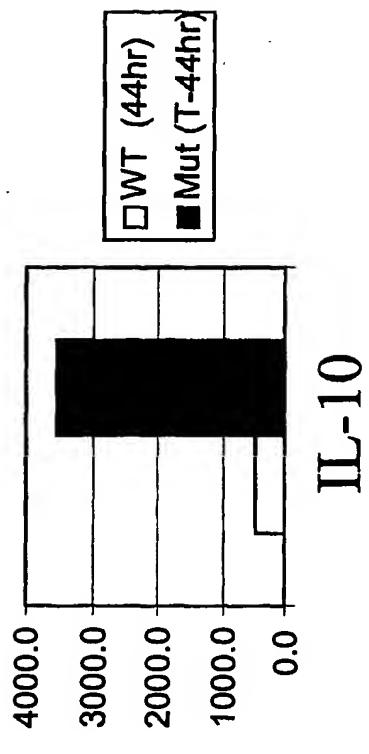


FIG. 10B

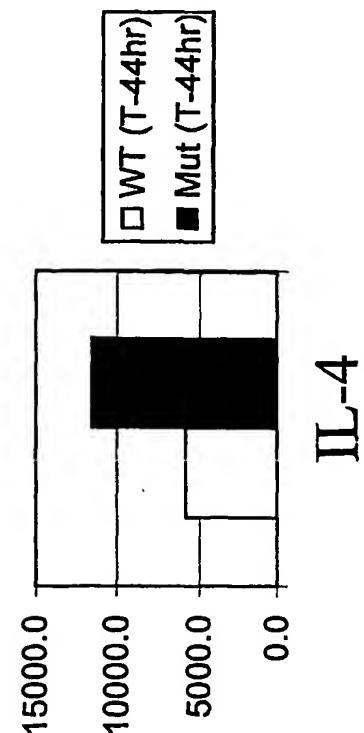


FIG. 10A

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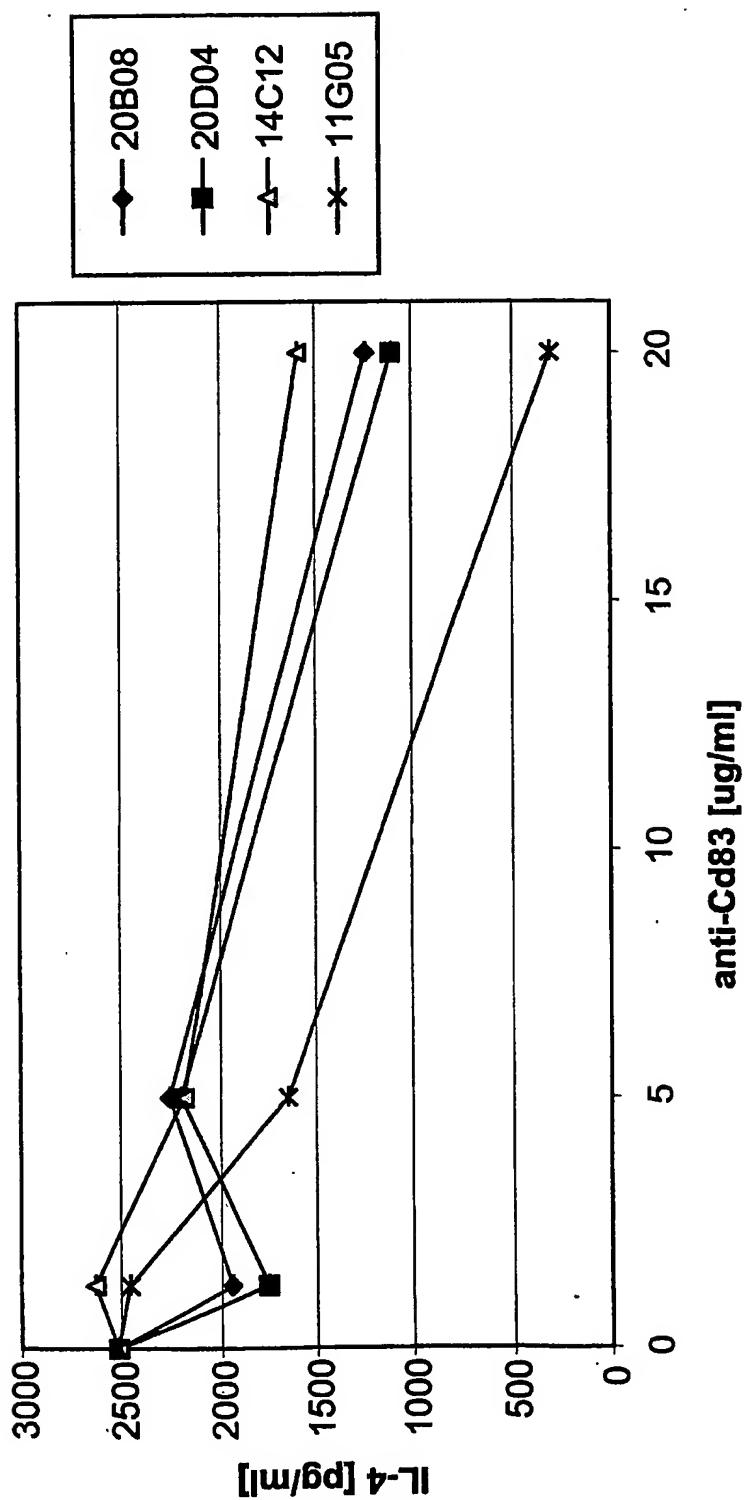


FIG. 11

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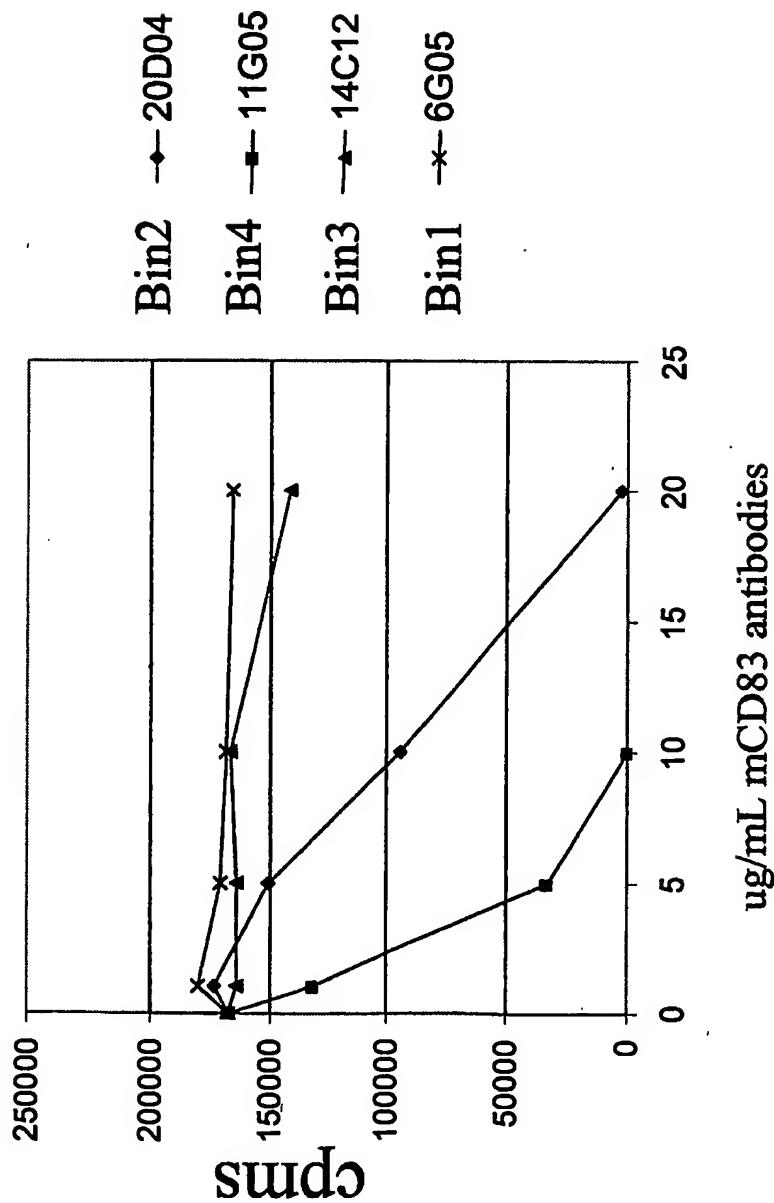


FIG. 12

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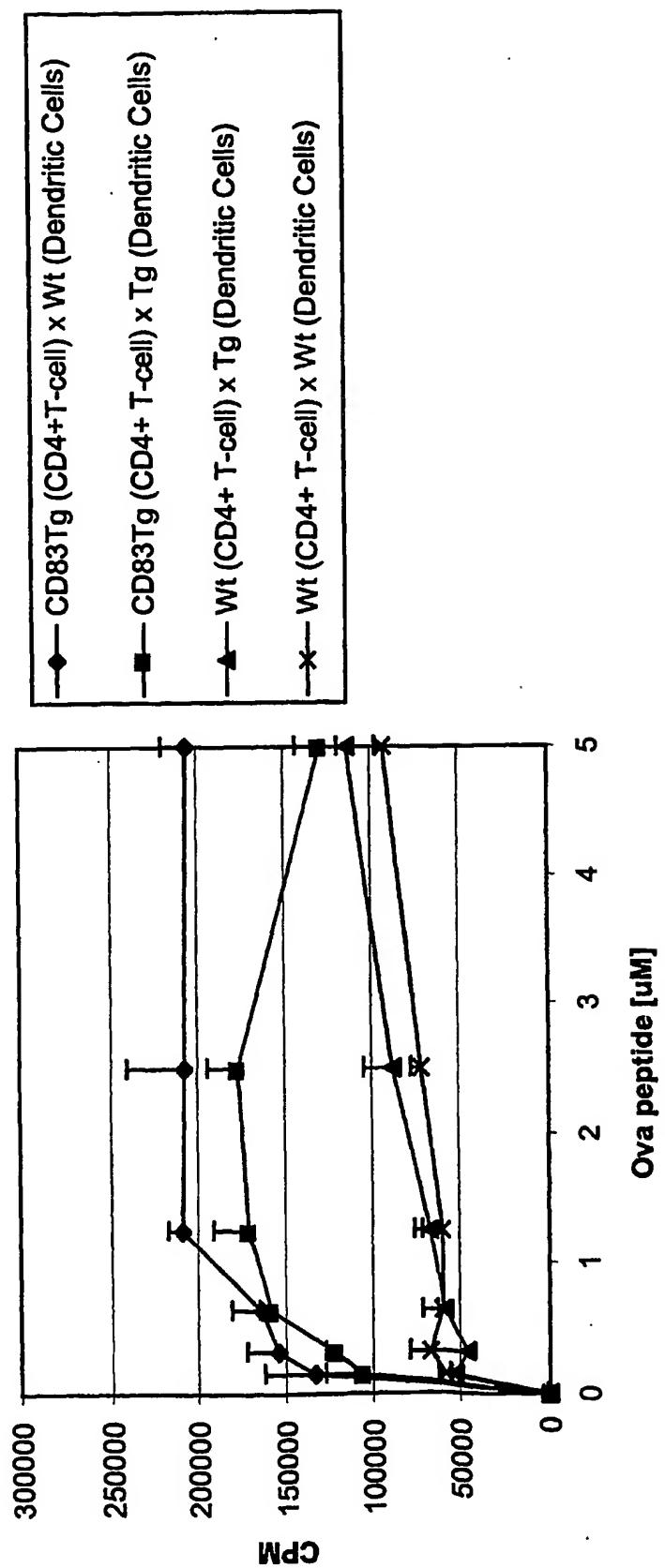


FIG. 13

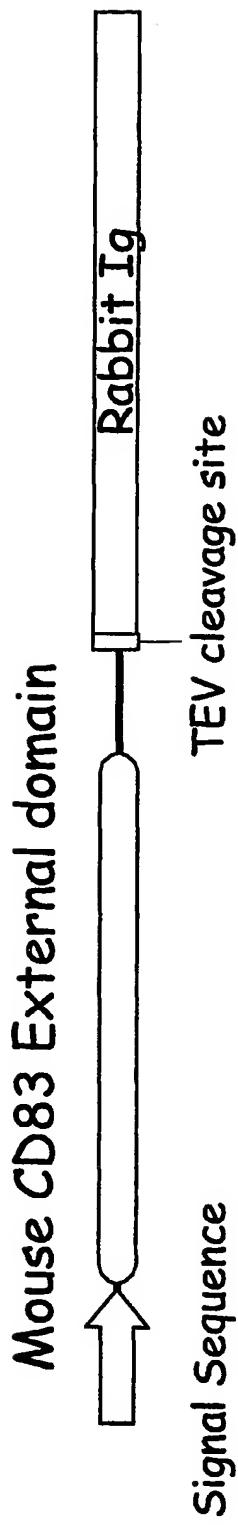


FIG. 14

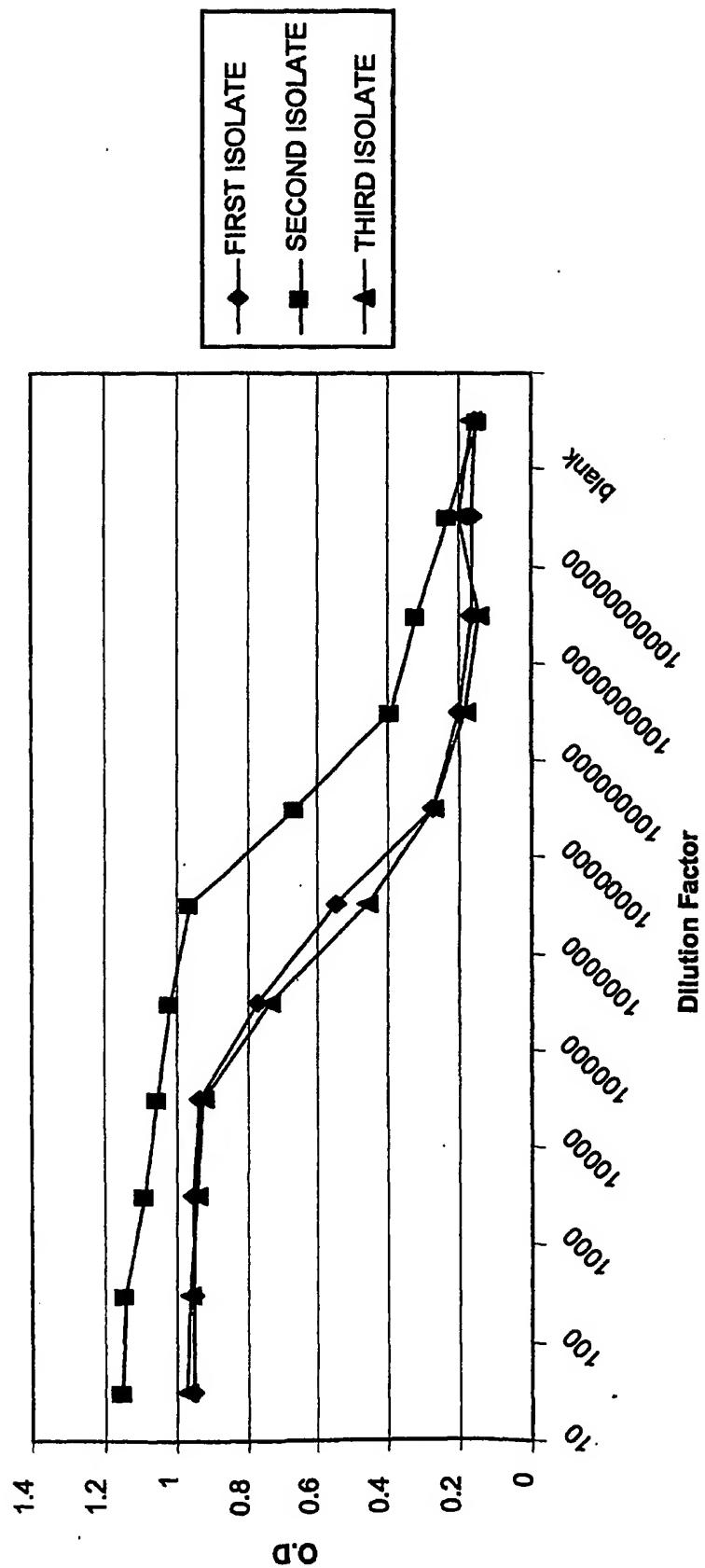


FIG. 15

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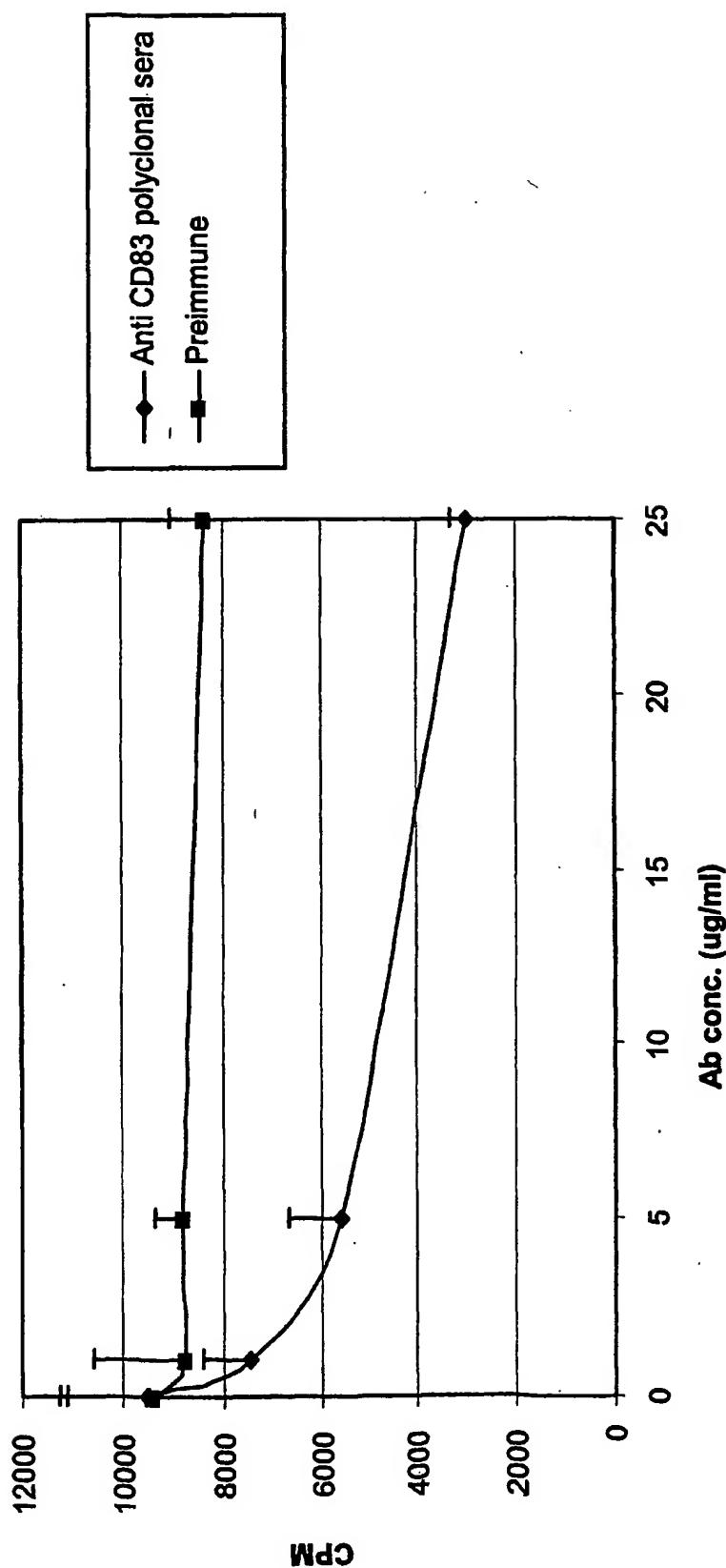


FIG. 16

	CDR1	CDR2	CDR3
20B08H	METGLRWILLVAVLKGVOQOQSVEESGGRLVTPGTLTCTVSGFSLISSYDMDTWRQAPGKGLEWIGLIYAS-	GSTYYASWAKGRFTISKTSTTVDLLEVTSLTEDTATYFC	PLAPCCGDTPSS
6G05H	METGLRWILLVAVLKGVOQOQSVEESGGRLVSPGTPLTCTAAGFSLISSYDMSWVRQAPGKGLEYIGIISSS-	TYFCREGAGVSMT---LWGPGTLTVSSGQPKAPS	PLAPCCGDTPSS
20D04H	METGLRWILLVAVLKGVOQOQSVEESGGRLVTPGTLTCTVSGFSLISSYDMSWVRQAPGKGLEWIGIYAS-	TFCAEDAGFSNA---LWGPGTLTVSSGQPKAPS	PLAPCCGDTPSS
11G05	METGLRWILLVAVLKGVOQOQSVEESGGRLVTPGTLTCTVSGFTISDYDLSWVRQAPGEGLKYGIFIAID-	TFCARGAGD-----LWGPGTLTVSSGQPKAPS	PLAPCCGDTPSS
14C12	METGLRWILLVAVLKGVOQHQSVEESGGRLVTPGTLTCTAAGFSSRSSYDMSWVRQAPGKGLEWVGVISTA-	YNSHYASWAKGRFTISRTSTTVDLKMTSLTTEDTATYFCARGGSWLD-----LWGQGTLTVSSGQPKAPS	
20B08H			PLAPCCGDTPSS
6G05H			PLAPCCGDTPSS
20D04H			PLAPCCGDTPSS
11G05			PLAPCCGDTPSS
14C12			PLAPCCGDTPSS

FIG. 17A

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	CDR1	CDR2	CDR3
20B08L	MDMRAPTQLLGLLLWLPGARC	-AYDMTQTPASVEAVGGTVTIKCQASQSISTY--	
6G05L	MDMRAPTQLLGLLLWLPGARC	-AYDMTQTPASVEAVGGTVAIKCQASQSIVSSY--	
20D04L	MDMRAPTQLLGLLLWLPGARC	ADVVMQTTPASVSAAVGGTVTINCQASESISNY--	
11G05L	MDTRAPTQLLGLLLWLPGARC	ADVVMQTTPASVSAAVGGTVTINCQSSSKNVYNNW	
14C12L	MDXRAPTQLLGLLLWLPGARC-A	LVMTQTPASVSAAVGGTVTINCQSSQSIVDNDDE	
20B08L	LDWYQQKPGQQPKLIIYDASDLASGVPSRFKGSSGTQFTLTISDLECADAAATYYCQQGGYT---		
6G05L	LAWYQQKPGQQPKPLIYEASMLAAGVSSRFKGSSGTDFLTISDLECDAAATYYCQQGGYS---		
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11G05L	LSWFQQKPGQQPKLIIYASTLASGVPSRFKGSSGTQFTLTISDVQCDDAATYYCAG-DYSS--S		
14C12L	LSWYQQKPGQQPKLIIYASKLIAASGVPSRFKGSSGTQFALTISGVQCDDAATYYCQATHYSS--D-		
20B08L	-HSNVDNVFGGGTEVVVKGDPVAPTVLIFPPSS		
6G05L	-ISDIDNAFFGGGTEVVVKGDPVAPTVLIFPPSS		
20D04L	KFISDGAAFFGGGTEVVVKGDPVAPTVLIFPPSS		
11G05L	SDNGFGGGTEVVVKGDPVAPTVLIFPPSS		
14C12L	-WYLTTFGGGTEVVVKGDPVAPTVLIFPPSS		

**FIG. 17B**

## SEQUENCE LISTING

<110> Appleby, MW

5 Proll, S

Paeper, B

Staehling-Hampton, K

<120> MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS

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<130> 1427.004W01

<150> US 60/331,958

<151> 2001-11-21

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gttcttgaag atatggacct aggggagcta ttgcgccacg acaggaggaa gttctcagat	1860
gttgcattga tgtaacatttgc ttgcatttct ttaatgagct gggctcccttc ctcatttgct	1920
tcccaaagag attttgcactaactaattgtt tgcccatcac ccacactatg aaagtaaaag	1980
15ggatgtgag cagatacagc gtgcttacact ctcagccatg actttcatgc tattaaaaga	2040
atgcatgtga a	2051

&lt;210&gt; 2

&lt;211&gt; 196

20&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 2

Met Ser Gln Gly Leu Gln Leu Leu Phe Leu Gly Cys Ala Cys Ser Leu			
25 1	5	10	15
Ala Pro Ala Met Ala Met Arg Glu Val Thr Val Ala Cys Ser Glu Thr			
20	25		30
Ala Asp Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Leu Ser Tyr Ala			
35	40	45	
30Val Ser Trp Ala Lys Val Ser Glu Ser Gly Thr Glu Ser Val Glu Leu			
50	55	60	
Pro Glu Ser Lys Gln Asn Ser Ser Phe Glu Ala Pro Arg Arg Arg Ala			
65	70	75	80
Tyr Ser Leu Thr Ile Gln Asn Thr Thr Ile Cys Ser Ser Gly Thr Tyr			
35	85	90	95
Arg Cys Ala Leu Gln Glu Leu Gly Gly Gln Arg Asn Leu Ser Gly Thr			
100	105	110	
Val Val Leu Lys Val Thr Gly Cys Pro Lys Glu Ala Thr Glu Ser Thr			
115	120	125	
40Phe Arg Lys Tyr Arg Ala Glu Ala Val Leu Leu Phe Ser Leu Val Val			
130	135	140	
Phe Tyr Leu Thr Leu Ile Ile Phe Thr Cys Lys Phe Ala Arg Leu Gln			

145	150	155	160
Ser Ile Phe Pro Asp Ile Ser Lys Pro Gly Thr Glu Gln Ala Phe Leu			
165	170	175	
Pro Val Thr Ser Pro Ser Lys His Leu Gly Pro Val Thr Leu Pro Lys			
5	180	185	190
Thr Glu Thr Val			
195			

&lt;210&gt; 3

10&lt;211&gt; 2051

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

15&lt;223&gt; Mutant CD83 sequence

&lt;400&gt; 3

gcgctccagc	cgcatgtcgc	aaggcctcca	gctcctgttt	ctaggctgcg	cctgcagcct	60
ggcaccccgcg	atggcgatgc	gggaggtgac	ggtggcttgc	tccgagaccg	ccgacttgcc	120
20ttgcacagcg	ccctgggacc	cgcagctctc	ctatgcagtg	tcctggcca	aggctccga	180
gagtggca	ct gaggatgg	agctcccga	gagcaagcaa	aacagctcct	tcgaggcccc	240
caggagaagg	gcctattccc	tgacgatcca	aaacactacc	atctgcagct	cgggcaccta	300
caggtgtgcc	ctgcaggagc	tcggagggca	g gc aacttg	agcggcaccc	t gttctgaa	360
ggtgacagga	tgccccaagg	aagctacaga	gtcaacttcc	aggaagtaca	ggcagaagc	420
25tgtgttgc	tc tt ct ct gg	ttgtttcta	cctgacactc	atcatttca	cctgcaaatt	480
tgcacgacta	caaagcattt	tcccagat	ttctaaacct	ggtacgaa	aagctttct	540
tccagtcacc	tcccaagca	aacatttggg	gccagtgacc	cttcctaaga	cagaaacgg	600
aagagttagga	tctccactgg	ttttacaaa	gccaagggca	catcagatca	gtgtgcctga	660
atgcaccccg	gacaagagaa	aatgagctc	catcctcaga	tggcaacctt	tcttgaagt	720
30ccttcacctg	acagtggct	ccacactact	ccctgacaca	gggtcttgag	caccatcata	780
tgatcacgaa	gcatggagta	tc accgcttc	tctgtggctg	tca gcttaat	gttcatgtg	840
gctatctgg	caacctcg	tg agtgc	tttgc	actcatctac	aagctatgg	900
tgaagcaggg	tcatggaaa	tttgaacact	ctgagctggc	cctgtgacag	actcctgagg	960
acagctgtcc	tctcctacat	ctgggataca	tctcttga	tttgcctgt	ttcggtgcac	1020
35cagcccagat	gtctcacatc	tggcgaaat	tgacaggcca	agctgtgagc	cagtggaaa	1080
tat tagcaa	ataatttccc	agtgc	agg	tctgtctatt	agtaaggagt	1140
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40gaaggtctag	ttacatagca	ttgctagctg	acaagcagcc	tgagagaaga	tggagaatgt	1380
tcctcaaaat	agggcagaca	agctagaagc	actgtacagt	gccctgctgg	gaagggcaga	1440
caatggactg	agaaaccaga	agtctggcca	caagattgtc	tgtatgattc	tggacgagtc	1500

acttgtggtt ttcactctct ggttagtaaa ccagatagtt tagtctgggt tgaatacaat	1560
ggatgtgaag ttgcttgggg aaagctgaat gtatgtaaata cattggcaac tctactggc	1620
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gttcttgaag atatggacct aggggagcta ttgcgccacg acaggaggaa gttctcagat	1860
gttgcattga tgtaaacatttgcatttgc ttaatgagct gggctccttc ctcatttgct	1920
tcccaaagag attttgcocca actaatggtg tgcccatcac ccacactatg aaagtaaaaag	1980
ggatgctgag cagatacagc gtgcttacct ctcagccatg actttcatgc tattaaaaga	2040
10atgcatgtga a	2051

&lt;210&gt; 4

&lt;211&gt; 251

&lt;212&gt; PRT

15&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Mutant CD83 sequence

20&lt;400&gt; 4

Met Ser Gln Gly Leu Gln Leu Leu Phe Leu Gly Cys Ala Cys Ser Leu			
1	5	10	15
Ala Pro Ala Met Ala Met Arg Glu Val Thr Val Ala Cys Ser Glu Thr			
20	25		30
25Ala Asp Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Leu Ser Tyr Ala			
35	40	45	
Val Ser Trp Ala Lys Val Ser Glu Ser Gly Thr Glu Ser Val Glu Leu			
50	55	60	
Pro Glu Ser Lys Gln Asn Ser Ser Phe Glu Ala Pro Arg Arg Arg Ala			
3065	70	75	80
Tyr Ser Leu Thr Ile Gln Asn Thr Thr Ile Cys Ser Ser Gly Thr Tyr			
85	90	95	
Arg Cys Ala Leu Gln Glu Leu Gly Gly Gln Arg Asn Leu Ser Gly Thr			
100	105	110	
35Val Val Leu Lys Val Thr Gly Cys Pro Lys Glu Ala Thr Glu Ser Thr			
115	120	125	
Phe Arg Lys Tyr Arg Ala Glu Ala Val Leu Leu Phe Ser Leu Val Val			
130	135	140	
Phe Tyr Leu Thr Leu Ile Ile Phe Thr Cys Lys Phe Ala Arg Leu Gln			
40145	150	155	160
Ser Ile Phe Pro Asp Ile Ser Lys Pro Gly Thr Glu Gln Ala Phe Leu			
165	170	175	

Pro Val Thr Ser Pro Ser Lys His Leu Gly Pro Val Thr Leu Pro Lys		
180	185	190
Thr Glu Thr Val Arg Val Gly Ser Pro Leu Val Phe Thr Lys Pro Arg		
195	200	205
5Ala His Gln Ile Ser Val Pro Glu Cys His Pro Asp Lys Arg Arg Met		
210	215	220
Ser Ser Ile Leu Arg Trp Gln Pro Phe Phe Glu Val Leu His Leu Thr		
225	230	235
Val Gly Ser Thr Leu Leu Pro Asp Thr Gly Ser		
10	245	250

&lt;210&gt; 5

&lt;211&gt; 756

&lt;212&gt; DNA

15&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Mutant CD83 sequence

20&lt;400&gt; 5

atgtcgcaag gcctccagct cctgtttcta ggctgcgcct gcagcctggc acccgcgatg	60
gcatgcggg aggtgacggt ggcttgctcc gagaccgccc acttgccttgc acacgcgcc	120
tgggaccgcg agcttcctta tgcagtgtcc tggccaagg tctccgagag tggactgag	180
agtgtggagc tcccgagag caagcaaaac agtccttcg aggccccag gagaagggcc	240
25tattccctga cgatccaaa cactaccatc tgcaagtcgg gcacccatc gtgtgcctg	300
caggagctcg gagggcagcg caacttgagc ggcaccgtgg ttctgaaggt gacaggatgc	360
cccaaggaag ctacagatc aactttcagg aagtacaggg cagaagctgt gttgctcttc	420
tctctggttg ttttctacct gacactcatc atttcacct gcaaatttgc acgactacaa	480
agcatttcc cagatatttc taaaccttgtt acggaacaag cttttcttcc agtcaccc	540
30ccaagcaaaac atttggggcc agtgaccctt cctaagacag aaacggttaag agtaggatct	600
ccactggttt ttacaaagcc aagggcacat cagatcagtg tgcctgaatg ccacccggac	660
aagagaagaa tgagctccat cctcagatgg caaccttct ttgaagtct tcacctgaca	720
gtgggctcca cactactccc tgacacaggg tcttga	756

35&lt;210&gt; 6

&lt;400&gt; 6

000

40&lt;210&gt; 7

&lt;211&gt; 168

&lt;212&gt; DNA

<213> Artificial Sequence

<220>

<223> Mutant CD83 sequence

5

<400> 7

agagtaggat ctccactgg ttttacaaag ccaagggcac atcagatcg tgcctgaa 60  
tgccacccgg acaagagaag aatgagctcc atcctcagat ggcaacctt cttgaagtc 120  
cttcacctga cagtgggctc cacactactc cctgacacag ggtcttga 168

10

<210> 8

<211> 55

<212> PRT

<213> Artificial Sequence

15

<220>

<223> Mutant CD83 sequence

<400> 8

20Arg Val Gly Ser Pro Leu Val Phe Thr Lys Pro Arg Ala His Gln Ile  
1 5 10 15  
Ser Val Pro Glu Cys His Pro Asp Lys Arg Arg Met Ser Ser Ile Leu  
20 25 30  
Arg Trp Gln Pro Phe Phe Glu Val Leu His Leu Thr Val Gly Ser Thr  
25 35 40 45  
Leu Leu Pro Asp Thr Gly Ser  
50 55

<210> 9

30<211> 205

<212> PRT

<213> Homo sapiens

<400> 9

35Met Ser Arg Gly Leu Gln Leu Leu Leu Ser Cys Ala Tyr Ser Leu  
1 5 10 15  
Ala Pro Ala Thr Pro Glu Val Lys Val Ala Cys Ser Glu Asp Val Asp  
20 25 30  
Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Val Pro Tyr Thr Val Ser  
40 35 40 45  
Trp Val Lys Leu Leu Glu Gly Gly Glu Glu Arg Met Glu Thr Pro Gln  
50 55 60

Glu Asp His Leu Arg Gly Gln His Tyr His Gln Lys Gly Gln Asn Gly  
 65 70 75 80  
 Ser Phe Asp Ala Pro Asn Glu Arg Pro Tyr Ser Leu Lys Ile Arg Asn  
 85 90 95  
 5Thr Thr Ser Cys Asn Ser Gly Thr Tyr Arg Cys Thr Leu Gln Asp Pro  
 100 105 110  
 Asp Gly Gln Arg Asn Leu Ser Gly Lys Val Ile Leu Arg Val Thr Gly  
 115 120 125  
 Cys Pro Ala Gln Arg Lys Glu Glu Thr Phe Lys Lys Tyr Arg Ala Glu  
 10 130 135 140  
 Ile Val Leu Leu Ala Leu Val Ile Phe Tyr Leu Thr Leu Ile Ile  
 145 150 155 160  
 Phe Thr Cys Lys Phe Ala Arg Leu Gln Ser Ile Phe Pro Asp Phe Ser  
 165 170 175  
 15Lys Ala Gly Met Glu Arg Ala Phe Leu Pro Val Thr Ser Pro Asn Lys  
 180 185 190  
 His Leu Gly Leu Val Thr Pro His Lys Thr Glu Leu Val  
 195 200 205

20<210> 10

<211> 2574

<212> DNA

<213> Homo sapiens

25<400> 10

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ggacgcgcac gcggcgaggc cggcggtga gccggggcg gggacgggg cggacgggg	120
gcgaaggggg cggggacggg ggcgcggcc ggcctaacgg gattaggagg gcgcgccacc	180
cgcttccgtc gcccgcggg gaatccccg ggtggcggcc agggaaatgc cccaaacggc	240
30gggcataaaaa gggcagccgc gccggcgccc cacagctctg cagctcggtt cagcggcgca	300
gcgcctccagc catgtcgccgc ggcctccagc ttctgtctt gagctgcgcc tacagcctgg	360
ctcccgccac gccggagggt aagggtggctt gtcggaaaga tgtggacttg ccctgcaccg	420
ccccctggga tccgcaggtt ccctacacgg tctcctgggt caagttattt gagggtgggt	480
aagagaggat ggagacaccc caggaagacc acctcagggg acagcactat catcagaagg	540
35ggcaaaaatgg ttcttcgac gcccccaatg aaaggcccta ttccctgttgg atccgaaaca	600
ctaccagctg caactcgccc acatacaggt gcactctgca ggacccggat gggcagagaa	660
acctaagtgg caaggtgatc ttgagagtga caggatgccc tgcacagcgt aaagaagaga	720
cttttaagaa atacagacgc gagattgtcc tgctgtggc tctggatttt ttctacttaa	780
cactcatcat tttcacttgt aagttgcac ggctacagag tatcttcca gattttcta	840
40aagctggcat ggaacgagct ttctccag ttacctcccc aaataagcat ttagggctag	900
tgactcctca caagacagaa ctggatgtgag caggattct gcaggttctt ctccctgaag	960
ctgaggctca ggggtgtgcc tgtctgttac actggaggag agaagaatga gcctacgctg	1020

aagatggcat	cctgtgaagt	ccttcaccc	actgaaaaca	tctggaaagg	gatcccaccc	1080				
cattttctgt	gggcaggcct	cgaaaaccat	cacatgacca	catagcatga	ggccactgt	1140				
gcttctccat	ggccaccc	tcagcgatgt	atgcagctat	ctggtaacc	tcctggacat	1200				
tttttcagtc	atataaaaagc	tatggtgaga	tgca	aaagggtctt	gggaaatatg	1260				
5aatgc	ccccca	gctggcccgt	gacagactcc	tgaggacagc	tgtcctcttc	tgcatcttgg	1320			
ggacatctct	ttgaattttc	tgtgtttgc	tgtaccagcc	cagatgttt	acgtctggga	1380				
gaaattgaca	gatcaagctg	tgagacagt	gaaatattt	agcaaataat	ttcctgggt	1440				
gaaggtcctg	ctattactaa	ggagtaatct	gtgtacaaag	aaataacaag	tcgatgaact	1500				
atcccccagc	agggtcttt	catctggaa	agacatccat	aaagaagcaa	taaagaagag	1560				
10tgccacattt	attttatat	ctatatgtac	ttgtcaaaga	aggttgtgt	ttttctgctt	1620				
ttgaaatctg	tatctgttagt	gagata	tgta	caggcagc	ggacatagag	1680				
agggagaaga	agtcagagag	ggtgacaaga	tagagagcta	ttaatggcc	ggctggaaat	1740				
gctgggctga	cgg	tgctgcagtc	tgggtgctcg	cccacttgc	ccactatctg	1800				
cttgagcaag	ttc	cttctctgg	tgtctgctt	ctccattgt	aaccacaagg	ctgtgc	1860			
15ggcta	atgaa	gatcatatac	gtgaaaatta	tttggaaaca	tataaagcac	tatacagatt	1920			
cgaaactcca	ttgagt	catt	tgatgtatgt	gttttggga	tgagagggt	1980				
ctatccattt	ctcatgtttt	ccattgtt	aaacaaagaa	ggttaccaag	aagc	cttcc	2040			
tgtagc	ttc	tgttaggaatt	cttttggga	agtgaggaag	ccaggtccac	ggtctgttct	2100			
tgaagc	gta	gccta	acaca	ctccaagata	tggacacacg	ggagccctg	2160			
20ctt	cacgaag	tgttgcat	atgttttagc	cattgttggc	tttcc	ttt	caaacttggg	2220		
cccttcc	ttt	tttcc	tttcc	aaaggcattt	attgctgagt	tatatgttca	ctgtcccc	2280		
aatattaggg	at	aaaaac	cg	atccaagtt	gatttagt	gtttac	ctgttgg	2340		
tcatgttatt	aaacgtat	gc	atgt	gagaa	gggtgtttt	ctgtttata	ttcaactcat	2400		
aagacttgg	gat	aggaaaaa	atg	agtaatg	gttactagc	ttaata	ccatgt	2460		
25taatctgtac	aac	gaaacccc	cat	gtatgtaa	gttac	ctat	gtaaca	aaacc	tgcacttata	2520
cccat	gtaact	taaaatgaaa	gtt	aaaaata	aaaaacat	ata	aca	aaaaata	aaaa	2574

&lt;210&gt; 11

&lt;211&gt; 239

30&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 11

Met	Asp	Met	Arg	Ala	Pro	Thr	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp		
35	1			5				10					15			
Leu	Pro	Gly	Ala	Arg	Cys	Ala	Asp	Val	Val	Met	Thr	Gln	Thr	Pro	Ala	
								20			25		30			
Ser	Val	Ser	Ala	Ala	Val	Gly	Gly	Thr	Val	Thr	Ile	Asn	Cys	Gln	Ala	
								35			40		45			
40	Ser	Glu	Ser	Ile	Ser	Asn	Tyr	Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
								50			55		60			
Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Arg	Thr	Ser	Thr	Leu	Ala	Ser	Gly	

65	70	75	80
Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu			
	85	90	95
Thr Ile Ser Gly Val Gln Cys Asp Asp Val Ala Thr Tyr Tyr Cys Gln			
5	100	105	110
Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala Phe Gly Gly			
	115	120	125
Gly Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu			
	130	135	140
10Leu Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile			
	145	150	155
Val Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu			
	165	170	175
Val Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro			
15	180	185	190
Gln Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu			
	195	200	205
Thr Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr			
	210	215	220
20Gln Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys			
	225	230	235

&lt;210&gt; 12

&lt;211&gt; 720

25&lt;212&gt; DNA

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 12

atggacatga gggcccccac tcagctgctg gggtcctgc tgctctggct cccaggtgcc	60
30agatgtcccg atgtcgtat gacccagact ccagcctccg tgcgtgcagc tggggaggc	120
acagtcacca tcaattgcca gccagtgaa agcatttagca actacttatac ctggtatcag	180
cagaaaccag ggcagcctcc caagctcctg atctacagga catccactct ggcatactggc	240
gtctcatcgc gttcaaagg cagtggatct gggacagagt acactctcac catcagcggc	300
gtcagtgtg acgatgttgc cacttactac tgtcaatgca cttctggtgg gaagttcatt	360
35agtgtatggc ctgtttcgg cggaggacc gaggtggtgg tcaaaggta tccagttca	420
cctactgtcc tcctcttcccc accatctagc gatgagggtgg caactggAAC agtcaccatc	480
gtgtgtgtgg cgaataaaata ctttcccgat gtccacgtca cctgggagggt ggatggcacc	540
acccaaacaa ctggcatcga gaacagtaaa acacccgcaga attctgcaga ttgtacctac	600
aacctcagca gcactctgac actgaccagc acacagtaca acagccacaa agagtacacc	660
40tgcaaggta cccagggcac gacctcagtc gtccagagct tcagtaggaa gaactgttaa	720

&lt;210&gt; 13

&lt;211&gt; 454

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

5&lt;400&gt; 13

Met	Glu	Thr	Gly	Leu	Arg	Trp	Leu	Leu	Leu	Val	Ala	Val	Leu	Lys	Gly
1				5				10				15			

Val	Gln	Cys	Gln	Ser	Val	Glu	Glu	Ser	Gly	Gly	Arg	Leu	Val	Thr	Pro
					20			25				30			

10	Gly	Thr	Pro	Leu	Thr	Leu	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Ser
	35						40				45					

Asn	Asn	Ala	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu
						50		55			60				

Trp	Ile	Gly	Tyr	Ile	Trp	Ser	Gly	Gly	Leu	Thr	Tyr	Tyr	Ala	Asn	Trp
1565					70				75				80		

Ala	Glu	Gly	Arg	Phe	Thr	Ile	Ser	Lys	Thr	Ser	Thr	Thr	Val	Asp	Leu
	85						90				95				

Lys	Met	Thr	Ser	Pro	Thr	Ile	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala
	100						105				110				

20	Arg	Gly	Ile	Asn	Asn	Ser	Ala	Leu	Trp	Gly	Pro	Gly	Thr	Leu	Val	Thr
	115							120			125					

Val	Ser	Ser	Gly	Gln	Pro	Lys	Ala	Pro	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro
	130						135				140					

Cys	Cys	Gly	Asp	Thr	Pro	Ser	Ser	Thr	Val	Thr	Leu	Gly	Cys	Leu	Val
25145							150			155			160		

Lys	Gly	Tyr	Leu	Pro	Glu	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Thr
	165							170			175				

Leu	Thr	Asn	Gly	Val	Arg	Thr	Phe	Pro	Ser	Val	Arg	Gln	Ser	Ser	Gly
	180							185			190				

30	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Ser	Val	Thr	Ser	Ser	Ser	Gln	Pro
	195						200				205					

Val	Thr	Cys	Asn	Val	Ala	His	Pro	Ala	Thr	Asn	Thr	Lys	Val	Asp	Lys
	210						215				220				

Thr	Val	Ala	Pro	Ser	Thr	Cys	Ser	Lys	Pro	Thr	Cys	Pro	Pro	Pro	Glu
35225							230			235			240		

Leu	Leu	Gly	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp
						245			250			255		

Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp
	260						265				270				

40	Val	Ser	Gln	Asp	Asp	Pro	Glu	Val	Gln	Phe	Thr	Trp	Tyr	Ile	Asn	Asn
	275							280			285					

Glu	Gln	Val	Arg	Thr	Ala	Arg	Pro	Pro	Leu	Arg	Glu	Gln	Gln	Phe	Asn
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

290	295	300
Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp		
305	310	315
Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro		
5	325	330
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu		
340	345	350
Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg		
355	360	365
10Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile		
370	375	380
Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr		
385	390	395
395	400	
Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys		
15	405	410
410	415	
Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys		
420	425	430
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile		
435	440	445
20Ser Arg Ser Pro Gly Lys		
450		

&lt;210&gt; 14

&lt;211&gt; 1362

25&lt;212&gt; DNA

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 14

atggagacag gcctgcgtcg	gcttcctcgt gtcgctgtgc	tcaaagggtgt ccagtgtcag	60
30tcgggtggagg agtccggggg	tcgcctggtc acgcctggga	caccctgac actcacctgc	120
accgtctctg gattctccct	cagtaacaat gcaataaaact	gggtccgcca ggctccaggg	180
aaggggctag agtggatcgg	atacatttg agtggtgggc	ttacatacta cgcaactgg	240
gccccggcc gattcaccat	ctccaaaacc tcgactacgg	tggatctgaa gatgaccagt	300
ccgacaatcg aggacacggc	cacctatttc tggccagag	ggattaataa ctccgctttg	360
35tggggcccaag gcacccttgt	caccgtctcc tcaaggcaac	ctaaggctcc atcagtcttc	420
ccactggccc cctgtcgccg	ggacacacccc tctagcacgg	tgaccttggg ctgcctggtc	480
aaaggctacc tcccgagcc	agtgaccgtg acctggaact	cgggcacct caccaatggg	540
gtacgcacct tcccgtccgt	ccggcagtcc tcaggcctct	actcgctgag cagcgtggtg	600
agcgtgacct caagcagcca	gccccgtcacc tgcaacgtgg	cccaccgcac cacaacacc	660
40aaaatggaca agaccgttgc	gccctcgaca tgcagcaagc	ccacgtgccc accccctgaa	720
ctcctggggg gaccgtctgt	cttcatcttc cccccaac	ccaaggacac cctcatgatc	780
tcacgcaccc ccgaggtcac	atgcgtggtg gtggacgtga	gccaggatga ccccgaggtg	840

cagttcacat ggtacataaa caacgagcag gtgcgcaccc cccggccgcc gctacggag 900  
 cagcagttca acagcacat ccgcgtggtc agcaccctcc ccatcgcgca ccaggactgg 960  
 ctgagggca aggagttcaa gtgcaaagtc cacaacaagg cactccggc ccccatcgag 1020  
 aaaaccatct ccaaagccag agggcagccc ctggagccga aggtctacac catggccct 1080  
 5ccccggagg agctgagcag caggtcggtc agcctgaccc gcatgatcaa cggttctac 1140  
 ccttccgaca tctcggtgga gtggagaag aacgggaagg cagaggacaa ctacaagacc 1200  
 acgcccggc tgctggacag cgacggctcc tacttcctct acaacaagct ctcagtgcac 1260  
 acgagtgagt ggcagcgggg cgacgtcttc acctgctccg tcatgcacga ggccttgcac 1320  
 aaccactaca cgcagaagtc catctccgc tctccggta aa 1362

10

&lt;210&gt; 15

&lt;211&gt; 238

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

15

&lt;400&gt; 15

Met	Asp	Thr	Arg	Ala	Pro	Thr	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp	
1								5			10				15	
Leu	Pro	Gly	Ala	Arg	Cys	Ala	Asp	Val	Val	Met	Thr	Gln	Thr	Pro	Ala	
20								20			25				30	
Ser	Val	Ser	Ala	Ala	Val	Gly	Gly	Thr	Val	Thr	Ile	Asn	Cys	Gln	Ser	
								35			40				45	
Ser	Lys	Asn	Val	Tyr	Asn	Asn	Trp	Leu	Ser	Trp	Phe	Gln	Gln	Lys		
								50			55				60	
25	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Tyr	Ala	Ser	Thr	Leu	Ala
								65			70				80	
Ser	Gly	Val	Pro	Ser	Arg	Phe	Arg	Gly	Ser	Gly	Ser	Gly	Thr	Gln	Phe	
								85			90				95	
Thr	Leu	Thr	Ile	Ser	Asp	Val	Gln	Cys	Asp	Asp	Ala	Ala	Thr	Tyr	Tyr	
30								100			105				110	
Cys	Ala	Gly	Asp	Tyr	Ser	Ser	Ser	Asp	Asn	Gly	Phe	Gly	Gly	Gly		
								115			120				125	
Thr	Glu	Val	Val	Val	Lys	Gly	Asp	Pro	Val	Ala	Pro	Thr	Val	Leu	Leu	
								130			135				140	
35	Phe	Pro	Pro	Ser	Ser	Asp	Glu	Val	Ala	Thr	Gly	Thr	Val	Thr	Ile	Val
								145			150				160	
Cys	Val	Ala	Asn	Lys	Tyr	Phe	Pro	Asp	Val	Thr	Val	Thr	Trp	Glu	Val	
								165			170				175	
Asp	Gly	Thr	Thr	Gln	Thr	Thr	Gly	Ile	Glu	Asn	Ser	Lys	Thr	Pro	Gln	
40								180			185				190	
Asn	Ser	Ala	Asp	Cys	Thr	Tyr	Asn	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Thr	
								195			200				205	

Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln  
 210 215 220

Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys  
 225 230 235

5

&lt;210&gt; 16

&lt;211&gt; 717

&lt;212&gt; DNA

&lt;213&gt; Oryctolagus cuniculus

10

&lt;400&gt; 16

atggacacca gggcccccac tcaagctgctg	gggctcctgc tgctctggct cccaggtgcc	60
agatgtcccg acgtcgtat gaccaggact ccagcctccg	tgtctgcagc tgtgggaggc	120
acagtccacca tcaattgcca gtccagtaag aatgtttata	ataacaactg gttatcctgg	180
15tttcagcaga aaccagggca gcctcccaag ctccctgatct	attatgcac cactctggca	240
tctgggtcc catcgcggtt cagaggcagt ggatctggga	cacagttcac tctcaccatt	300
agcgacgtgc agtgtacga tgctgccact tactactgtg	caggcgatta tagtagtagt	360
agtgataatg gtttcggcgg agggaccgag gtgggtggtca	aagggtatcc agttgcacct	420
actgtcctcc tcttcccacc atctagcgat gaggtggcaa	ctggAACAGT caccatcgtg	480
20tgtgtggcga ataaataactt tcccgatgtc accgtcacct	gggaggtgga tggcaccacc	540
caaacaactg gcatcgagaa cagtaaaaca ccgcagaatt	ctgcagattg tacctacaac	600
ctcagcagca ctctgacact gaccaggcaca cagtacaaca	gccacaaaga gtacacctgc	660
aagggtgaccc agggcacgac ctcagtcgtc cagagcttca	gtaggaagaa ctgttaa	717

25&lt;210&gt; 17

&lt;211&gt; 452

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

30&lt;400&gt; 17

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly			
1	5	10	15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro		
20	25	30

35Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Ile Ser		
35	40	45

Asp Tyr Asp Leu Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Lys		
50	55	60

Tyr Ile Gly Phe Ile Ala Ile Asp Gly Asn Pro Tyr Tyr Ala Thr Trp			
4065	70	75	80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu		
85	90	95

Lys Ile Thr Ala Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala  
           100                       105                       110  
 Arg Gly Ala Gly Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser  
           115                       120                       125  
 5Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro Cys Cys  
           130                       135                       140  
 Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val Lys Gly  
           145                       150                       155                       160  
 Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr Leu Thr  
   10                       165                       170                       175  
 Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly Leu Tyr  
           180                       185                       190  
 Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro Val Thr  
           195                       200                       205  
 15Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys Thr Val  
           210                       215                       220  
 Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu Leu Leu  
           225                       230                       235                       240  
 Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu  
   20                       245                       250                       255  
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser  
           260                       265                       270  
 Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn Glu Gln  
           275                       280                       285  
 25Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn Ser Thr  
           290                       295                       300  
 Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp Leu Arg  
           305                       310                       315                       320  
 Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro Ala Pro  
   30                       325                       330                       335  
 Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu Pro Lys  
           340                       345                       350  
 Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg Ser Val  
           355                       360                       365  
 35Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile Ser Val  
           370                       375                       380  
 Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr Thr Pro  
           385                       390                       395                       400  
 Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys Leu Ser  
   40                       405                       410                       415  
 Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys Ser Val  
           420                       425                       430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile Ser Arg

435 440 445

Ser Pro Gly Lys

450

5

<210> 18

<211> 1356

<212> DNA

<213> Oryctolagus cuniculus

10

<400> 18

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tcgggtggagg agtccggggg tcgcctggtc acgcctggga caccctgtac actcacctgc	120
acagtctctg gattcaccat cagtgactac gacttgagct gggtccgcca ggctccaggg	180
15gaggggctga aatacatcgg attcattgct attgatggta acccatacta cgcgacctgg	240
gcaaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa aatcaccgct	300
ccgacaacctg aagacacggc cacgtatttc tgtgccagag gggcagggga cctctggggc	360
ccagggaccc tcgtcacccgt ctcttcaggg caacctaagg ctccatcagt ctccccactg	420
gccccctgct gcggggacac accctcttagc acggtgacct tgggtgcct ggtcaaaggc	480
20 tacctcccg agccagtgac cgtgacctgg aactcgggca ccctcaccaa tgggtacgc	540
accttcccgt ccgtccggca gtcctcaggc ctctactcgc tgagcagcgt ggtgagcgtg	600
acctcaagca gccagcccgta cactgtcaac gtggcccacc cagccaccaa caccaaagtg	660
gacaagaccc ttgcgcctc gacatgcagg aagcccacgt gcccacccccc tgaactcctg	720
gggggaccgt ctgtcttcat ctccccccca aaacccaagg acaccctcat gatctcacgc	780
25 acccccgagg tcacatcggt ggtggtgac gtgagccagg atgacccga ggtcagttc	840
acatggtaca taaacaaca gcaagggtgcgc accgccccggc cgccgctacg ggagcagcag	900
ttcaacagca cgatcccggt ggtcagcacc ctccccatcg cgccacccagg ctggctgagg	960
ggcaaggagt tcaagtgcaa agtccacaac aaggcactcc cggcccccatt cgagaaaacc	1020
atctccaaag ccagaggcca gcccctggag ccgaagggtct acaccatggg ccctccccgg	1080
30 gagggagctga gcagcagggtc ggtcagcctg acctgcattga tcaacggctt ctacccttcc	1140
gacatctcggt tggagtggga gaagaacggg aaggcagagg acaactacaa gaccacggcc	1200
gccgtgctgg acagcgtacgg ctccctacttc ctctacaaca agctctcagt gcccacccgt	1260
gagtgccacgt ggggcacgt cttcacctgc tccgtgatgc acgaggcctt gcacaaccac	1320
tacacgcaga agtccatctc ccgctctccg ggtaaa	1356

35

<210> 19

<211> 238

<212> PRT

<213> Oryctolagus cuniculus

40

<220>

<221> SITE

<222> (1)...(238)

<223> Xaa = any amino acid

<400> 19

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 1 5 10 . 15  
 Leu Pro Gly Ala Arg Cys Ala Leu Val Met Thr Gln Thr Pro Ala Ser  
 20 25 30  
 Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser  
 10 35 40 45  
 Gln Ser Val Tyr Asp Asn Asp Glu Leu Ser Trp Tyr Gln Gln Lys Pro  
 50 55 60  
 Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Lys Leu Ala Ser  
 65 70 75 80  
 15Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Ala  
 85 90 95  
 Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys  
 100 105 110  
 Gln Ala Thr His Tyr Ser Ser Asp Trp Tyr Leu Thr Phe Gly Gly Gly  
 20 115 120 125  
 Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu  
 130 135 140  
 Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val  
 145 150 155 160  
 25Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val  
 165 170 175  
 Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln  
 180 185 190  
 Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr  
 30 195 200 205  
 Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln  
 210 215 220  
 Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys  
 225 230 235  
 35  
 <210> 20  
 <211> 717  
 <212> DNA  
 <213> Oryctolagus cuniculus  
 40  
 <400> 20  
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agatgtgccc ttgtgatgac ccagactcca gcctccgtgt ctgcagctgt gggaggcaca 120  
 gtcaccatca attgccatc cagtcagatgttatac acgacgaaatt atcctggtat 180  
 cagcagaaac cagggcagcc tcccaagctc ctgatctatc tggcatccaa gttggcatct 240  
 ggggtccccat cccgattcaa aggcatgga tctggacac agttcgctct caccatcagc 300  
 5ggcgtgcagt gtgacgatgc tgccacttac tactgtcaag ccactcatta tagtagtgat 360  
 tggtatctta ctteggcgg agggaccgag gtgggtgtca aaggtgatcc agttgcacct 420  
 actgtcctcc tcttcccacc atctagcgat gaggtggcaa ctggAACAGT caccatcg 480  
 tgtgtggcga ataaaactt tcccgatgtc accgtcacct gggaggtgga tggcaccacc 540  
 caaacaactg gcatcgagaa cagtaaaaca ccgcagaatt ctgcagattg tacctacaac 600  
 10ctcagcagca ctctgacact gaccagcaca cagtacaaca gccacaaaga gtacacctgc 660  
 aaggtgaccc agggcacgac ctcagtcgtc cagagcttca gtaggaagaa ctgttaa 717

&lt;210&gt; 21

&lt;211&gt; 454

15&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 21

Met	Glu	Thr	Gly	Leu	Arg	Trp	Leu	Leu	Leu	Val	Ala	Val	Leu	Lys	Gly
20	1			5			10			15					
Val	His	Cys	Gln	Ser	Val	Glu	Glu	Ser	Gly	Gly	Arg	Leu	Val	Thr	Pro
					20			25			30				
Gly	Thr	Pro	Leu	Thr	Leu	Thr	Cys	Thr	Ala	Ser	Gly	Phe	Ser	Arg	Ser
			35				40			45					
25Ser	Tyr	Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu
			50			55			60						
Trp	Val	Gly	Val	Ile	Ser	Thr	Ala	Tyr	Asn	Ser	His	Tyr	Ala	Ser	Trp
	65				70			75			80				
Ala	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Thr	Ser	Thr	Thr	Val	Asp	Leu
30				85			90			95					
Lys	Met	Thr	Ser	Leu	Thr	Thr	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala
				100			105			110					
Arg	Gly	Gly	Ser	Trp	Leu	Asp	Leu	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr
				115			120			125					
35Val	Ser	Ser	Gly	Gln	Pro	Lys	Ala	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro
				130			135			140					
Cys	Cys	Gly	Asp	Thr	Pro	Ser	Ser	Thr	Val	Thr	Leu	Gly	Cys	Leu	Val
145					150				155			160			
Lys	Gly	Tyr	Leu	Pro	Glu	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Thr
40				165			170			175					
Leu	Thr	Asn	Gly	Val	Arg	Thr	Phe	Pro	Ser	Val	Arg	Gln	Ser	Ser	Gly
				180			185			190					

Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro  
     195                     200                     205  
 Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys  
     210                     215                     220  
 5Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu  
     225                     230                     235                     240  
 Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp  
     245                     250                     255  
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp  
 10                       260                     265                     270  
 Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn  
     275                     280                     285  
 Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn  
     290                     295                     300  
 15Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp  
     305                     310                     315                     320  
 Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro  
     325                     330                     335  
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu  
 20                       340                     345                     350  
 Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg  
     355                     360                     365  
 Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile  
     370                     375                     380  
 25Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr  
     385                     390                     395                     400  
 Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys  
     405                     410                     415  
 Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys  
 30                       420                     425                     430  
 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile  
     435                     440                     445  
 Ser Arg Ser Pro Gly Lys  
     450  
 35  
 <210> 22  
 <211> 1362  
 <212> PRT  
 <213> Oryctolagus cuniculus  
 40  
 <400> 22  
 Ala Thr Gly Gly Ala Gly Ala Cys Ala Gly Gly Cys Cys Thr Gly Cys

19

1	5	10	15
Gly Cys Thr Gly Gly Cys Thr Thr Cys Thr Cys Cys Thr Gly Gly Thr			
20	25	30	
Cys Gly Cys Thr Gly Thr Cys Thr Cys Ala Ala Ala Gly Gly Thr			
5	35	40	45
Gly Thr Cys Cys Ala Cys Thr Gly Thr Cys Ala Gly Thr Cys Gly Gly			
50	55	60	
Thr Gly Gly Ala Gly Ala Gly Thr Cys Cys Gly Gly Gly Gly			
65	70	75	80
10Thr Cys Cys Cys Thr Gly Gly Thr Cys Ala Cys Gly Cys Cys Thr			
85	90	95	
Gly Gly Gly Ala Cys Ala Cys Cys Cys Thr Gly Ala Cys Ala Cys			
100	105	110	
Thr Cys Ala Cys Cys Thr Gly Cys Ala Cys Ala Gly Cys Cys Thr Cys			
115	120	125	
Thr Gly Gly Ala Thr Thr Cys Thr Cys Cys Gly Cys Ala Gly Cys			
130	135	140	
Ala Gly Cys Thr Ala Cys Gly Ala Cys Ala Thr Gly Ala Gly Cys Thr			
145	150	155	160
20Gly Gly Gly Thr Cys Cys Gly Cys Cys Ala Gly Gly Cys Thr Cys Cys			
165	170	175	
Ala Gly Gly Ala Ala Gly Gly Gly Cys Thr Gly Gly Ala Ala			
180	185	190	
Thr Gly Gly Thr Cys Gly Gly Ala Gly Thr Cys Ala Thr Thr Ala			
195	200	205	
Gly Thr Ala Cys Thr Gly Cys Thr Thr Ala Thr Ala Ala Cys Thr Cys			
210	215	220	
Ala Cys Ala Cys Thr Ala Cys Gly Cys Gly Ala Gly Cys Thr Gly Gly			
225	230	235	240
30Gly Cys Ala Ala Ala Ala Gly Gly Cys Cys Gly Ala Thr Thr Cys Ala			
245	250	255	
Cys Cys Ala Thr Cys Thr Cys Cys Ala Gly Ala Ala Cys Cys Thr Cys			
260	265	270	
Gly Ala Cys Cys Ala Cys Gly Gly Thr Gly Gly Ala Thr Cys Thr Gly			
275	280	285	
Ala Ala Ala Ala Thr Gly Ala Cys Cys Ala Gly Thr Cys Thr Gly Ala			
290	295	300	
Cys Ala Ala Cys Cys Gly Ala Ala Gly Ala Cys Ala Cys Gly Gly Cys			
305	310	315	320
40Cys Ala Cys Cys Thr Ala Thr Thr Cys Thr Gly Thr Gly Cys Cys			
325	330	335	
Ala Gly Ala Gly Gly Gly Thr Ala Gly Thr Thr Gly Gly Thr			

	340	345	350
	Thr Gly Gly Ala Thr Cys Thr Cys Thr Gly Gly Gly Cys Cys Ala		
	355	360	365
	Gly Gly Gly Cys Ala Cys Cys Cys Thr Gly Gly Thr Cys Ala Cys Cys		
5	370	375	380
	Gly Thr Cys Thr Cys Cys Thr Cys Ala Gly Gly Cys Ala Ala Cys		
	385	390	395
	Cys Thr Ala Ala Gly Gly Cys Thr Cys Cys Ala Thr Cys Ala Gly Thr		
	405	410	415
	10Cys Thr Thr Cys Cys Ala Cys Thr Gly Gly Cys Cys Cys Cys Cys		
	420	425	430
	Thr Gly Cys Thr Gly Cys Gly Gly Gly Ala Cys Ala Cys Ala Cys		
	435	440	445
	Cys Cys Thr Cys Thr Ala Gly Cys Ala Cys Gly Gly Thr Gly Ala Cys		
15	450	455	460
	Cys Thr Thr Gly Gly Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys		
	465	470	475
	Ala Ala Ala Gly Gly Cys Thr Ala Cys Cys Thr Cys Cys Cys Gly Gly		
	485	490	495
	20Ala Gly Cys Cys Ala Gly Thr Gly Ala Cys Cys Gly Thr Gly Ala Cys		
	500	505	510
	Cys Thr Gly Gly Ala Ala Cys Thr Cys Gly Gly Cys Ala Cys Cys		
	515	520	525
	Cys Thr Cys Ala Cys Cys Ala Ala Thr Gly Gly Gly Thr Ala Cys		
25	530	535	540
	Gly Cys Ala Cys Cys Thr Thr Cys Cys Cys Gly Thr Cys Cys Gly Thr		
	545	550	555
	Cys Cys Gly Gly Cys Ala Gly Thr Cys Cys Thr Cys Ala Gly Gly Cys		
	565	570	575
	30Cys Thr Cys Thr Ala Cys Thr Cys Gly Cys Thr Gly Ala Gly Cys Ala		
	580	585	590
	Gly Cys Gly Thr Gly Gly Thr Gly Ala Gly Cys Gly Thr Gly Ala Cys		
	595	600	605
	Cys Thr Cys Ala Ala Gly Cys Ala Gly Cys Cys Ala Gly Cys Cys Cys		
35	610	615	620
	Gly Thr Cys Ala Cys Cys Thr Gly Cys Ala Ala Cys Gly Thr Gly Gly		
	625	630	635
	Cys Cys Cys Ala Cys Cys Cys Ala Gly Cys Cys Ala Cys Cys Ala Ala		
	645	650	655
	40Cys Ala Cys Cys Ala Ala Gly Thr Gly Gly Ala Cys Ala Ala Gly		
	660	665	670
	Ala Cys Cys Gly Thr Thr Gly Cys Gly Cys Cys Thr Cys Gly Ala		

675	680	685
Cys Ala Thr Gly Cys Ala Gly Cys Ala Ala Gly Cys Cys Cys Ala Cys		
690	695	700
Gly Thr Gly Cys Cys Cys Ala Cys Cys Cys Cys Cys Thr Gly Ala Ala		
5705	710	715
Cys Thr Cys Cys Thr Gly Gly Gly Ala Cys Cys Gly Thr		
725	730	735
Cys Thr Gly Thr Cys Thr Thr Cys Ala Thr Cys Thr Thr Cys Cys Cys		
740	745	750
10Cys Cys Cys Ala Ala Ala Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys		
755	760	765
Ala Cys Cys Cys Thr Cys Ala Thr Gly Ala Thr Cys Thr Cys Ala Cys		
770	775	780
Gly Cys Ala Cys Cys Cys Cys Gly Ala Gly Gly Thr Cys Ala Cys		
15785	790	795
Ala Thr Gly Cys Gly Thr Gly Gly Thr Gly Gly Ala Cys		
805	810	815
Gly Thr Gly Ala Gly Cys Cys Ala Gly Gly Ala Thr Gly Ala Cys Cys		
820	825	830
20Cys Cys Gly Ala Gly Gly Thr Gly Cys Ala Gly Thr Thr Cys Ala Cys		
835	840	845
Ala Thr Gly Gly Thr Ala Cys Ala Thr Ala Ala Ala Cys Ala Ala Cys		
850	855	860
Gly Ala Gly Cys Ala Gly Gly Thr Gly Cys Gly Cys Ala Cys Cys Gly		
25865	870	875
Cys Cys Cys Gly Gly Cys Cys Gly Cys Cys Gly Cys Thr Ala Cys Gly		
885	890	895
Gly Gly Ala Gly Cys Ala Gly Cys Ala Gly Thr Thr Cys Ala Ala Cys		
900	905	910
30Ala Gly Cys Ala Cys Gly Ala Thr Cys Cys Gly Cys Gly Thr Gly Gly		
915	920	925
Thr Cys Ala Gly Cys Ala Cys Cys Cys Thr Cys Cys Cys Ala Thr		
930	935	940
Cys Gly Cys Gly Cys Ala Cys Cys Ala Gly Gly Ala Cys Thr Gly Gly		
35945	950	955
Cys Thr Gly Ala Gly Gly Gly Cys Ala Ala Gly Gly Ala Gly Thr		
965	970	975
Thr Cys Ala Ala Gly Thr Gly Cys Ala Ala Ala Gly Thr Cys Cys Ala		
980	985	990
40Cys Ala Ala Cys Ala Ala Gly Gly Cys Ala Cys Thr Cys Cys Cys Gly		
995	1000	1005
Gly Cys Cys Cys Cys Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala		

1010	1015	1020
Cys Cys Ala Thr Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Gly		
1025	1030	1035
Ala Gly Gly Gly Cys Ala Gly Cys Cys Cys Cys Thr Gly Gly Ala Gly		
5	1045	1050
Cys Cys Gly Ala Ala Gly Gly Thr Cys Thr Ala Cys Ala Cys Cys Ala		
1060	1065	1070
Thr Gly Gly Gly Cys Cys Cys Thr Cys Cys Cys Gly Gly Gly Ala		
1075	1080	1085
10Gly Gly Ala Gly Cys Thr Gly Ala Gly Cys Ala Gly Cys Ala Gly Gly		
1090	1095	1100
Thr Cys Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys Cys Thr		
1105	1110	1115
Gly Cys Ala Thr Gly Ala Thr Cys Ala Ala Cys Gly Gly Cys Thr Thr		
15	1125	1130
Cys Thr Ala Cys Cys Cys Thr Thr Cys Cys Gly Ala Cys Ala Thr Cys		
1140	1145	1150
Thr Cys Gly Gly Thr Gly Gly Ala Gly Thr Gly Gly Ala Gly Ala		
1155	1160	1165
20Ala Gly Ala Ala Cys Gly Gly Ala Ala Gly Gly Cys Ala Gly Ala		
1170	1175	1180
Gly Gly Ala Cys Ala Ala Cys Thr Ala Cys Ala Ala Gly Ala Cys Cys		
1185	1190	1195
Ala Cys Gly Cys Cys Gly Gly Cys Cys Gly Thr Gly Cys Thr Gly Gly		
25	1205	1210
Ala Cys Ala Gly Cys Gly Ala Cys Gly Gly Cys Thr Cys Cys Thr Ala		
1220	1225	1230
Cys Thr Thr Cys Cys Thr Cys Thr Ala Cys Ala Ala Cys Ala Ala Gly		
1235	1240	1245
30Cys Thr Cys Thr Cys Ala Gly Thr Gly Cys Cys Cys Ala Cys Gly Ala		
1250	1255	1260
Gly Thr Gly Ala Gly Thr Gly Gly Cys Ala Gly Cys Gly Gly Gly Gly		
1265	1270	1275
Cys Gly Ala Cys Gly Thr-Cys Thr Thr Cys Ala Cys Cys Thr Gly Cys		
35	1285	1290
Thr Cys Cys Gly Thr Gly Ala Thr Gly Cys Ala Cys Gly Ala Gly Gly		
1300	1305	1310
Cys Cys Thr Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala		
1315	1320	1325
40Cys Ala Cys Gly Cys Ala Gly Ala Ala Gly Thr Cys Cys Ala Thr Cys		
1330	1335	1340
Thr Cys Cys Cys Gly Cys Thr Cys Thr Cys Cys Gly Gly Gly Thr Ala		

23

1345	1350	1355	1360
Ala	Ala		

5<210> 23  
<211> 5  
<212> PRT  
<213> Oryctolagus cuniculus

10<400> 23  
Ser Tyr Asp Met Thr  
1 5

<210> 24  
15<211> 5  
<212> PRT  
<213> Oryctolagus cuniculus

<400> 24  
20Ser Tyr Asp Met Ser  
1 5

<210> 25  
<211> 5  
25<212> PRT  
<213> Oryctolagus cuniculus

<400> 25  
Asp Tyr Asp Leu Ser  
30 1 5

<210> 26  
<211> 5  
<212> PRT  
35<213> Oryctolagus cuniculus

<400> 26  
Ser Tyr Asp Met Ser  
1 5

40  
<210> 27  
<211> 8

<212> PRT

<213> Oryctolagus cuniculus

<400> 27

5Tyr Ala Ser Gly Ser Thr Tyr Tyr

1 5

<210> 28

<211> 8

10<212> PRT

<213> Oryctolagus cuniculus

<400> 28

Ser Ser Ser Gly Thr Thr Tyr Tyr

15 1 5

<210> 29

<211> 8

<212> PRT

20<213> Oryctolagus cuniculus

<400> 29

Tyr Ala Ser Gly Ser Thr Tyr Tyr

1 5

25

<210> 30

<211> 8

<212> PRT

<213> Oryctolagus cuniculus

30

<400> 30

Ala Ile Asp Gly Asn Pro Tyr Tyr

1 5

35<210> 31

<211> 8

<212> PRT

<213> Oryctolagus cuniculus

40<400> 31

Ser Thr Ala Tyr Asn Ser His Tyr

1 5

<210> 32  
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5  
<400> 32  
Glu His Ala Gly Tyr Ser Gly Asp Thr Gly His  
1 5 10

10<210> 33  
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15<400> 33  
Glu Gly Ala Gly Val Ser Met Thr  
1 5

<210> 34  
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<400> 34  
25Glu Asp Ala Gly Phe Ser Asn Ala  
1 5

<210> 35  
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<213> Oryctolagus cuniculus

<400> 35  
Gly Ala Gly Asp  
35 1

<210> 36  
<211> 6  
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40<213> Oryctolagus cuniculus

<400> 36

Gly Gly Ser Trp Leu Asp  
1 5

<210> 37  
5<211> 5  
<212> PRT  
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<400> 37  
10Arg Cys Ala Tyr Asp  
1 5

<210> 38  
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15<212> PRT  
<213> Oryctolagus cuniculus

<400> 38  
Arg Cys Ala Asp Val Val  
20 1 5

<210> 39  
<211> 5  
<212> PRT  
25<213> Oryctolagus cuniculus

<400> 39  
Arg Cys Ala Leu Val  
1 5  
30  
<210> 40  
<211> 6  
<212> PRT  
<213> Oryctolagus cuniculus

35  
<400> 40  
Gln Ser Ile Ser Thr Tyr  
1 5

40<210> 41  
<211> 6  
<212> PRT

<213> Oryctolagus cuniculus

<400> 41

Gln Ser Val Ser Ser Tyr

5 1 5

<210> 42

<211> 6

<212> PRT

10<213> Oryctolagus cuniculus

<400> 42

Glu Ser Ile Ser Asn Tyr

1 5

15

<210> 43

<211> 8

<212> PRT

<213> Oryctolagus cuniculus

20

<400> 43

Lys Asn Val Tyr Asn Asn Asn Trp

1 5

25<210> 44

<211> 12

<212> PRT

<213> Oryctolagus cuniculus

30<400> 44

Gln Gln Gly Tyr Thr His Ser Asn Val Asp Asn Val

1 5 10

<210> 45

35<211> 12

<212> PRT

<213> Oryctolagus cuniculus

<400> 45

40Gln Gln Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala

1 5 10

<210> 46

<211> 14

<212> PRT

<213> Oryctolagus cuniculus

5

<400> 46

Gln Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala

1 5 10

10<210> 47

<211> 11

<212> PRT

<213> Oryctolagus cuniculus

15<400> 47

Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly

1 5 10

<210> 48

20<211> 12

<212> PRT

<213> Oryctolagus cuniculus

<400> 48

25Gln Ala Thr His Tyr Ser Ser Asp Trp Leu Thr Tyr

1 5 10

<210> 49

<211> 5

30<212> RNA

<213> Artificial Sequence

<220>

<223> AU-rich sequence

35

<400> 49

auuua

5

<210> 50

40<211> 6

<212> RNA

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; AU-rich sequence

&lt;400&gt; 50

5auuuua

6

&lt;210&gt; 51

&lt;211&gt; 7

&lt;212&gt; RNA

10&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; AU-rich sequence

15&lt;400&gt; 51

auuuuua

7

&lt;210&gt; 52

&lt;211&gt; 157

20&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 52

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly

25 1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro

20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser

35 40 45

30Ser Tyr Asp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu

50 55 60

Trp Ile Gly Ile Ile Tyr Ala Ser Gly Ser Thr Tyr Tyr Ala Ser Trp

65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu

35 85 90 95

Glu Val Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ser

100 105 110

Arg Glu His Ala Gly Tyr Ser Gly Asp Thr Gly His Leu Trp Gly Pro

115 120 125

40Gly Thr Leu Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val

130 135 140

Phe Pro Leu Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser

30

145 150 155

&lt;210&gt; 53

&lt;211&gt; 154

5&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 53

Met	Glu	Thr	Gly	Leu	Arg	Trp	Leu	Leu	Leu	Val	Ala	Val	Leu	Lys	Gly	
10	1			5			10			15						
Val	Gln	Cys	Gln	Ser	Val	Glu	Glu	Ser	Gly	Gly	Arg	Leu	Val	Ser	Pro	
				20			25			30						
Gly	Thr	Pro	Leu	Thr	Leu	Thr	Cys	Thr	Ala	Ser	Gly	Phe	Ser	Leu	Ser	
				35			40			45						
15	Ser	Tyr	Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu
				50			55			60						
Tyr	Ile	Gly	Ile	Ile	Ser	Ser	Ser	Gly	Thr	Thr	Tyr	Tyr	Tyr	Ala	Asn	Trp
	65				70			75			80					
Ala	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Lys	Thr	Ser	Thr	Thr	Thr	Val	Asp	Leu
20					85			90			95					
Lys	Val	Thr	Ser	Pro	Thr	Ile	Gly	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala	
					100			105			110					
Arg	Glu	Gly	Ala	Gly	Val	Ser	Met	Thr	Leu	Trp	Gly	Pro	Gly	Thr	Leu	
					115			120			125					
25	Val	Thr	Val	Ser	Ser	Gly	Gln	Pro	Lys	Ala	Pro	Ser	Val	Phe	Pro	Leu
					130			135			140					
Ala	Pro	Cys	Cys	Gly	Asp	Thr	Pro	Ser	Ser							
145					150											

30&lt;210&gt; 54

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

35&lt;400&gt; 54

Met	Glu	Thr	Gly	Leu	Arg	Trp	Leu	Leu	Leu	Val	Ala	Val	Leu	Lys	Gly	
1				5			10			15						
Val	Gln	Cys	Gln	Ser	Val	Glu	Glu	Ser	Gly	Gly	Arg	Leu	Val	Thr	Pro	
				20			25			30						
40	Gly	Thr	Pro	Leu	Thr	Leu	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Ser
				35			40			45						
Ser	Tyr	Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	

50	55	60
Trp Ile Gly Ile Ile Tyr Ala Ser Gly Ser Thr Tyr Tyr Ala Ser Trp		
65	70	75
Ala Lys Gly Arg Val Ala Ile Ser Lys Thr Ser Thr Thr Val Asp Leu		80
5	85	90
Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala		95
100	105	110
Arg Glu Asp Ala Gly Phe Ser Asn Ala Leu Trp Gly Pro Gly Thr Leu		
115	120	125
10Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu		
130	135	140
Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser		
145	150	

15<210> 55  
 <211> 147  
 <212> PRT  
 <213> Oryctolagus cuniculus

20<400> 55			
Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp			
1	5	10	15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser			
20	25	30	
25Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser			
35	40	45	
Gln Ser Ile Ser Thr Tyr Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gln			
50	55	60	
Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val			
3065	70	75	80
Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr			
85	90	95	
Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln			
100	105	110	
35Gly Tyr Thr His Ser Asn Val Asp Asn Val Phe Gly Gly Thr Glu			
115	120	125	
Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro			
130	135	140	
Pro Ser Ser			
40145			

&lt;211&gt; 147

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

5&lt;400&gt; 56

Met	Asp	Met	Arg	Ala	Pro	Thr	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp		
1								5					10		15	
Leu	Pro	Gly	Ala	Arg	Cys	Ala	Tyr	Asp	Met	Thr	Gln	Thr	Pro	Ala	Ser	
									20				25		30	
10	Val	Glu	Val	Ala	Val	Gly	Gly	Thr	Val	Ala	Ile	Lys	Cys	Gln	Ala	Ser
									35				40		45	
Gln	Ser	Val	Ser	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	
									50				55		60	
15	Pro	Pro	Lys	Pro	Leu	Ile	Tyr	Glu	Ala	Ser	Met	Leu	Ala	Ala	Gly	Val
1565									70				75		80	
Ser	Ser	Arg	Phe	Lys	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	
									85				90		95	
100	Ile	Ser	Asp	Leu	Glu	Cys	Asp	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln
									100				105		110	
20	Gly	Tyr	Ser	Ile	Ser	Asp	Ile	Asp	Asn	Ala	Phe	Gly	Gly	Gly	Thr	Glu
									115				120		125	
130	Val	Val	Val	Lys	Gly	Asp	Pro	Val	Ala	Pro	Thr	Val	Leu	Leu	Phe	Pro
									130				135		140	
25	Pro	Ser	Ser													
145																

25145

&lt;210&gt; 57

&lt;211&gt; 150

&lt;212&gt; PRT

30&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 57

Met	Asp	Met	Arg	Ala	Pro	Thr	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp		
1								5					10		15	
35	Leu	Pro	Gly	Ala	Arg	Cys	Ala	Asp	Val	Val	Met	Thr	Gln	Thr	Pro	Ala
									20				25		30	
Ser	Val	Ser	Ala	Ala	Val	Gly	Gly	Thr	Val	Thr	Ile	Asn	Cys	Gln	Ala	
									35				40		45	
40	Ser	Glu	Ser	Ile	Ser	Asn	Tyr	Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
									50				55		60	
65	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Arg	Thr	Ser	Thr	Leu	Ala	Ser	Gly
									70				75		80	

Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu  
                   85                  90                  95  
 Thr Ile Ser Gly Val Gln Cys Asp Asp Val Ala Thr Tyr Tyr Cys Gln  
                   100              105              110  
 5Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala Phe Gly Gly  
                   115              120              125  
 Gly Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu  
                   130              135              140  
 Leu Phe Pro Pro Ser Ser  
 10145                          150

<210> 58

<211> 236

<212> PRT

15<213> Oryctolagus cuniculus

<400> 58

Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Trp  
     1              5                  10              15  
 20Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser  
     20              25                  30  
 Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser  
     35              40              45  
 Gln Ser Ile Ser Thr Tyr Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gln  
 25      50              55              60  
 Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val  
     65              70              75              80  
 Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr  
     85              90              95  
 30Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln  
     100              105              110  
 Gly Tyr Thr His Ser Asn Val Asp Asn Val Phe Gly Gly Thr Glu  
     115              120              125  
 Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro  
 35      130              135              140  
 Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val Cys Val  
     145              150              155              160  
 Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val Asp Gly  
     165              170              175  
 40Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln Asn Ser  
     180              185              190  
 Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr Ser Thr

195	200	205
Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln Gly Thr		
210	215	220
Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys		
5225	230	235

&lt;210&gt; 59

&lt;211&gt; 711

&lt;212&gt; DNA

10&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 59

atggacatga gggcccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc	60
agatgtgcct atgatatatgac ccagactcca gcctctgtgg aggttagctgt gggaggcaca	120
15gtcaccatca agtgcagggc cagtcaagagc attagtagtacct acttagactg gtatcagcag	180
aaaccagggc agcctcccaa gctcctgatc tatgtatgcat ccgatctggc atctggggtc	240
ccatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat cagcgcacctg	300
gagtgtgcgg atgctgccac ttactactgt caacagggtt atacacatag taatgttgat	360
aatgttttcg gcgaggggac cgaggtgggtg gtcaaagggtg atccagggtgc acctactgtc	420
20ctcctttcc caccatctag cgatgaggtg gcaactggaa cagtcaccat cgtgtgtgt	480
gcgaataaat actttcccgta tgtcaccgtc acctgggagg tggatggcac cacccaaaca	540
actggcatcg agaacagtaa aacaccgcag aattctgcag attgtaccta caacctcage	600
ageactctga cactgaccag cacacagttac aacagccaca aagagtacac ctgcaagggtg	660
acccaggcga cgacctcagt cgtccagagc ttccatggaa agaactgtta a	711

25

&lt;210&gt; 60

&lt;211&gt; 456

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

30

&lt;400&gt; 60

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly

1 5 10 15

Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro

35 20 25 30

Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser

35 40 45

Ser Tyr Asp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu

50 55 60

40Trp Ile Gly Ile Ile Tyr Ala Ser Gly Thr Thr Tyr Tyr Ala Asn Trp

65 70 75 80

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu

35

	85	90	95
Lys Val Thr Ser Pro Thr Ile Gly Asp Thr Ala Thr Tyr Phe Cys Ala			
	100	105	110
Arg Glu Gly Ala Gly Val Ser Met Thr Leu Trp Gly Pro Gly Thr Leu			
5	115	120	125
Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu			
	130	135	140
Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys			
145	150	155	160
10Leu Val Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser			
	165	170	175
Gly Thr Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser			
	180	185	190
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser			
15	195	200	205
Gln Pro Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val			
	210	215	220
Asp Lys Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro			
225	230	235	240
20Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro			
	245	250	255
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val			
	260	265	270
Val Asp Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile			
25	275	280	285
Asn Asn Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln			
	290	295	300
Phe Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln			
305	310	315	320
30Asp Trp Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala			
	325	330	335
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro			
	340	345	350
Leu Glu Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser			
35	355	360	365
Ser Arg Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser			
	370	375	380
Asp Ile Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr			
385	390	395	400
40Lys Thr Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr			
	405	410	415
Asn Lys Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe			

420	425	430
Thr Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys		
435	440	445
Ser Ile Ser Arg Ser Pro Gly Lys		
5 450	455	

&lt;210&gt; 61

&lt;211&gt; 1368

&lt;212&gt; DNA

10&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 61

atggagacag gcctgcgctg gcttccctg gtcgctgtgc tcaaagggtgt ccagtgtcag	60
tcggtgagg agtccgggg tcgcctggc acgcctggga caccctgac actcacctgc	120
15acagtctcg gattccctc cagcagctac gacatgacct gggtccgcca ggctccaggg	180
aaggggctgg aatggatcg aatcatttat gctagtggta ccacatacta cgcaactgg	240
gcgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgaa agtcaccagt	300
ccgacaatcg gggacacggc cacctatttc tgtgccagag agggggctgg tggtagtatg	360
actttgtggg gcccaggcac cctggtcacc gtctccctc tag gcaacctaa ggctccatca	420
20gtctccccac tggcccccctg ctgcggggac acaccctcta gcacggtgac cttggcgtgc	480
ctggtcaaag gctacccccc ggagccagtg accgtgacct ggaactcggg caccctcacc	540
aatgggtac gcacccccc gtccgtccgg cagtcctcag gcctctactc gctgagcgc	600
gtggtgagcg tgacctcaag cagccagccc gtcacctgca acgtggccca cccagccacc	660
aacaccaaag tggacaagac cgttgcgccc tcgacatgca gcaagccac gtggccaccc	720
25cctgaactcc tggggggacc gtctgtcttc atctccccca caaaacccaa ggacacccctc	780
atgtatccac gcacccccc ggtcacatgc gtggtggtgg acgtgagcca ggatgacccc	840
gaggtgcagt tcacatggta cataaacaac gagcagggtgc gcacccccc gccgccccta	900
cgggagcgc agttcaacag cacgatccgc gtggtcagca ccctccccat cgccgaccag	960
gactggctga gggcaagga gttcaagtgc aaagtccaca acaaggcact cccggccccc	1020
30atcgagaaaa ccacatccaa agccagaggg cagcccccgg agccgaaggt ctacaccatg	1080
ggccctcccc gggaggagct gagcagcagg tcgggtcagcc tgacccgtcat gatcaacggc	1140
ttctaccctt ccgacatctc ggtggagtgg gagaagaacg ggaaggcaga ggacaactac	1200
aagaccacgc cggccgtgt ggacagcgc ggcctctact tcctctacaa caagctctca	1260
gtgcccacga gtgagtggca gcggggcgcac gtcttcaccc gtcgggtgat gcacgaggcc	1320
35ttgcacaacc actacacgcgca gaagtccatc tcccgctctc cgggtaaa	1368

&lt;210&gt; 62

&lt;211&gt; 236

&lt;212&gt; PRT

40&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 62

Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Trp  
 1 5 10 15  
 Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser  
 20 25 30  
 5Val Glu Val Ala Val Gly Gly Thr Val Ala Ile Lys Cys Gln Ala Ser  
 35 40 45  
 Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln  
 50 55 60  
 Pro Pro Lys Pro Leu Ile Tyr Glu Ala Ser Met Leu Ala Ala Gly Val  
 1065 70 75 80  
 Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr  
 85 90 95  
 Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln  
 100 105 110  
 15Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala Phe Gly Gly Thr Glu  
 115 120 125  
 Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro  
 130 135 140  
 Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val Cys Val  
 20145 150 155 160  
 Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val Asp Gly  
 165 170 175  
 Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln Asn Ser  
 180 185 190  
 25Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr Ser Thr  
 195 200 205  
 Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln Gly Thr  
 210 215 220  
 Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys  
 30225 230 235

&lt;210&gt; 63

&lt;211&gt; 711

&lt;212&gt; DNA

35&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 63

atggacatga	gggccccac	tcaactgctg	gggctccgtc	tgctctggct	cccaggtgcc	60
agatgtgcct	atgatatgac	ccagactcca	gcctctgtgg	aggttagctgt	gggaggcaca	120
40gtcgccatca	agtgccaggc	cagtcagagc	gttagtagtt	acttagcctg	gtatcagcag	180
aaaccagggc	agcctcccaa	gcccctgatc	tacgaagcat	ccatgctggc	ggctgggtc	240
tcatcgcggt	tcaaaggcag	tggatctggg	acagacttca	ctctcaccat	cagcgacctg	300

gagtgtgacg atgctgccac ttactattgt caacagggtt attctatcag tgatattgat	360
aatgctttcg gcggaggac cgaggtgtg gtcaaaggta atccagtgc acctactgtc	420
ctcctttcc caccatctag cgatgagggt gcaactggaa cagtccacat cgtgtgtg	480
gcgaataaaat actttcccga tgtcaccgtc acctgggagg tggatggcac cacccaaaca	540
5actggcatcg agaacagtaa aacaccgcag aattctgcag attgtaccta caacctcagc	600
agcactctga cactgaccag cacacagtac aacagccaca aagagtacac ctgcaagggt	660
acccaggcga cgacctcagt cgtccagac ttcaqtagga agaactgtta a	711

<210> 64

10<211> 459

<212> PRT

<213> Oryctolagus cuniculus

<400> 64

15Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly  
 1 5 10 15  
 Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Ser Pro  
 20 25 30  
 Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser  
 20 35 40 45  
 Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu  
 50 55 60  
 Tyr Ile Gly Ile Ile Ser Ser Ser Gly Ser Thr Tyr Tyr Ala Ser Trp  
 65 70 75 80  
 25Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu  
 85 90 95  
 Glu Val Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ser  
 100 105 110  
 Arg Glu His Ala Gly Tyr Ser Gly Asp Thr Gly His Leu Trp Gly Pro  
 30 115 120 125  
 Gly Thr Leu Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val  
 130 135 140  
 Phe Pro Leu Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr  
 145 150 155 160  
 35Leu Gly Cys Leu Val Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr  
 165 170 175  
 Trp Asn Ser Gly Thr Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val  
 180 185 190  
 Arg Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr  
 40 195 200 205  
 Ser Ser Ser Gln Pro Val Thr Cys Asn Val Ala His Pro Ala Thr Asn  
 210 215 220

Thr Lys Val Asp Lys Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr  
 225                    230                    235                    240  
 Cys Pro Pro Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro  
 245                    250                    255  
 5Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr  
 260                    265                    270  
 Cys Val Val Val Asp Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr  
 275                    280                    285  
 Trp Tyr Ile Asn Asn Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg  
 10    290                    295                    300  
 Glu Gln Gln Phe Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile  
 305                    310                    315                    320  
 Ala His Gln Asp Trp Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His  
 325                    330                    335  
 15Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg  
 340                    345                    350  
 Gly Gln Pro Leu Glu Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu  
 355                    360                    365  
 Glu Leu Ser Ser Arg Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe  
 20    370                    375                    380  
 Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu  
 385                    390                    395                    400  
 Asp Asn Tyr Lys Thr Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr  
 405                    410                    415  
 25Phe Leu Tyr Asn Lys Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly  
 420                    425                    430  
 Asp Val Phe Thr Cys Ser Val Met His Glu Ala Leu His Asn His Tyr  
 435                    440                    445  
 Thr Gln Lys Ser Ile Ser Arg Ser Pro Gly Lys  
 30    450                    455

&lt;210&gt; 65

&lt;211&gt; 1377

&lt;212&gt; DNA

35&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 65

atggagacag	gcctgcgtg	gcttctcctg	gtcgctgtgc	tcaaagggtt	ccagtgtcag	60
tcggggagg	agtccggggg	tcgcctggc	tcgcctggg	caccctgac	actcacctgc	120
40acagcctctg	gattctccct	cagtagctac	gacatgagct	gggtccgcca	ggctccaggg	180
aaggggctgg	aatacatcg	aatcattagt	atagtggtt	gcacatacta	cgcgagctgg	240
gcgaaaggcc	gattcaccat	ctccaaaacc	tcgaccacgg	tggatctgga	agtgaccagt	300

ctgacaaccg aggacacggc cacatttc ttagtagag aacatgtgg ttatagtgg	360
gatacgggtc acttgtgggg cccaggcacc ctggtcaccc ttcctcgaa gcaacctaag	420
gctccatcag tcttcccact ggccccctgc tgccccgaca caccctctag cacggtgacc	480
ttgggctgcc tggtaaaagg ctacctcccg gagccagtga ccgtgacccg gaactcgaa	540
5accctcacca atgggtacg cacccctccg tccgtccggc agtcctcagg cctctactcg	600
ctgagcagcg tggtgagcgt gacctaagc agccagcccg tcacctgaa cgtggccac	660
ccagccacca acaccaaagt ggacaagacc gttgcgcct cgacatgcag caagccacg	720
tgcccacccc ctgaactcct ggggggaccc tctgtcttca tcttcccccc aaaacccaag	780
gacaccctca tcatctcagc caccctccg gtcacatcg tggtggtggc cgtgagccag	840
10gatgaccccg aggtgcagtt cacatggta ataaacaacg agcaggtgcg caccggccgg	900
ccggcgtac gggagcagca gttcaacagc acgatccgcg tggtcagcac cctcccccac	960
gcccaccagg actggctgag gggcaaggag ttcaagtgc aagtccacaa caaggcactc	1020
ccggccccca tcgagaaaac catctccaaa gccagaggc agccctggc gccaaggc	1080
tacaccatgg gcccctcccg ggaggagctg agcagcaggt cggtcagcct gacctgcatt	1140
15atcaacggct tctacccttc cgacatctcg gtggagtggg agaagaacgg gaaggcagag	1200
gacaactaca agaccacgcc ggccgtctg gacagcagc gctcctactt cctctacaac	1260
aagctctcag tgcccacagag ttagtggcag cggggcgcacg tcttcacctg ctccgtgatg	1320
cacgaggcct tgcacaacca ctacacgcag aagtccatct cccgctctcc ggtaaa	1377

20&lt;210&gt; 66

&lt;211&gt; 150

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

25&lt;400&gt; 66

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly			
1	5	10	15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro			
20	25	30	
30Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Ile Ser			
35	40	45	
Asp Tyr Asp Leu Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Lys			
50	55	60	
Tyr Ile Gly Phe Ile Ala Ile Asp Gly Asn Pro Tyr Tyr Ala Thr Trp			
3565	70	75	80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu			
85	90	95	
Lys Ile Thr Ala Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala			
100	105	110	
40Arg Gly Ala Gly Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser			
115	120	125	
Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro Cys Cys			

41

130	135	140
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Gly Asp Thr Pro Ser Ser		
145	150	

5&lt;210&gt; 67

&lt;211&gt; 152

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

10&lt;400&gt; 67

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly			
1	5	10	15

Val His Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro			
20	25	30	

15Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Arg Ser			
35	40	45	

Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu			
50	55	60	

Trp Val Gly Val Ile Ser Thr Ala Tyr Asn Ser His Tyr Ala Ser Trp			
2065	70	75	80

Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu			
85	90	95	

Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala			
100	105	110	

25Arg Gly Gly Ser Trp Leu Asp Leu Trp Gly Gln Gly Thr Leu Val Thr			
115	120	125	

Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro			
130	135	140	

Cys Cys Gly Asp Thr Pro Ser Ser			
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30145	150		
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&lt;210&gt; 68

&lt;211&gt; 149

&lt;212&gt; PRT

&lt;213&gt; Oryctolagus cuniculus

&lt;400&gt; 68

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Trp			
1	5	10	15

40Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala			
20	25	30	

Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser			
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42

35	40	45
Ser Lys Asn Val Tyr Asn Asn Asn Trp Leu Ser Trp Phe Gln Gln Lys		
50	55	60
Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala		
565	70	75
Ser Gly Val Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Gln Phe		
85	90	95
Thr Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr		
100	105	110
10Cys Ala Gly Asp Tyr Ser Ser Ser Asp Asn Gly Phe Gly Gly Gly		
115	120	125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu		
130	135	140
Phe Pro Pro Ser Ser		
15145		

&lt;210&gt; 69

&lt;211&gt; 149

&lt;212&gt; PRT

20&lt;213&gt; Oryctolagus cuniculus

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)...(149)

25&lt;223&gt; Xaa = any amino acid

&lt;400&gt; 69

Met Asp Xaa Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Trp			
1	5	10	15

30Leu Pro Gly Ala Arg Cys Ala Leu Val Met Thr Gln Thr Pro Ala Ser			
20	25	30	

Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser			
35	40	45	

Gln Ser Val Tyr Asp Asn Asp Glu Leu Ser Trp Tyr Gln Gln Lys Pro			
35	50	55	60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Lys Leu Ala Ser			
65	70	75	80

Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Ala			
85	90	95	

40Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys			
100	105	110	

Gln Ala Thr His Tyr Ser Ser Asp Trp Tyr Leu Thr Phe Gly Gly Gly			
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43

115

120

125

Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu

130

135

140

Phe Pro Pro Ser Ser

5145